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EPIDEMIOLOGY AND PUBLIC HEALTH

EPIDEMIOLOGY AND PUBLIC HEALTH

A Text and Reference Book for Physicians, Medical
Students and Health Workers

IN THREE VOLUMES

BY

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VOL. II

NUTRITIONAL DISORDERS
ALIMENTARY INFECTIONS
PERCUTANEOUS INFECTIONS

ST. LOUIS

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EPIDEMIOLOGY AND PUBLIC HEALTH

VOLUME II

CHAPTER I INTRODUCTION

The arrangement adopted in Volume I has been continued in this. An attempt has been made to group the diseases according to the avenues through which the virus reaches and infects the body. This attempt has been only partially successful. There are some epidemic diseases for which there is no specific virus and there are others in which the avenues of infection may be multiple. A rough classification of the diseases discussed in this volume appears as follows: (1) Nutritional disorders. (2) Alimentary infections. (3) Percutaneous infections.

We have not hesitated to include in a work on epidemiology certain nutritional disorders, such as scurvy and beriberi, but there are diseases, the classification of which has not been finally and conclusively determined. We are thinking now of rickets and pellagra. That infection with a living organism is not considered in the causation of scurvy and beriberi at present seems quite certain, although this conclusion may be invalidated by future investigation. Just how large a part is played in the development of pellagra and rickets by an unbalanced diet we are not able at present to say. Likewise, we are still very much in the dark as to infection in the development of goitre. There has always been before us the big subject of the relation between malnutrition and susceptibility to infection. At present we are ready to admit our ignorance on many points.

That food poisoning is, for the most part at least, due to infection of the food seems to be no longer doubtful. The infecting organism in the food may continue to grow and multiply in the animal body or it may, outside the body, produce a toxin to which all deleterious effects are due. There is a tendency at present to attribute all forms of food poisoning to the bacillus botulinus. This is certainly an error. There can be no doubt that there are many bacteria in the colon-typhoid group,

including the paratyphoids, which may so alter foods outside the body that speedy effects follow eating, or, in other cases, a real infection may develop. Food poisoning due to putrefactive changes in the food before this is taken into the body is now very rare compared with what it was 30 or 40 years ago. This is due to the greater care given to the preparation and care of food. Especially is this true of milk and milk products.

We have taken occasion in this volume to repeatedly call attention to the difference in scope between epidemiology and bacteriology. We have tried to show that the former is much broader and embraces the latter. In the chapter on Asiatic cholera we have dwelt upon the fact that the epidemiology of this disease was quite worked out and sufficiently well known to form the basis of rules and regulations by which the progress of the disease was arrested long before the specific vibrio had been discovered. This is true of other diseases as well. When it was shown early in the nineteenth century that the spread of typhoid fever depends solely upon the disposition of the fecal discharges of the infected person the main point in the epidemiology of this disease was solved. It is true in both typhoid fever and Asiatic cholera that bacteriology has enabled us, first, to recognize promptly and with certainty the disease, and, in the second place, to detect carriers.

We are quite aware of the fact that we have not done justice to the animal parasitic infestations. These are not of so much importance in this as in certain other countries, but we would have liked to have gone more fully into them had space permitted.

Following out the plan we announced in the first volume we are leaving the venereal diseases and public health administration for the third volume. Possibly we may be able to include certain local infections in that volume.

In the preparation of this volume we have enjoyed the facilities of the Library of the Surgeon General. In utilizing these books we are indebted for many courtesies to Major General Merritte W. Ireland, Surgeon General United States Army, Brigadier General Robert E. Noble, Librarian, and to Assistant Librarians Neumann, Tucker, Martin and Hall. Colonel Charles F. Craig has kindly read the chapters on typhoid fever, dysentery, and malaria, to all of which subjects he has made valuable original contributions. The chapter on relapsing fever has been read by Professor Frederick G. Novy, of the University of Michigan, whose name will always be prominently identified with the fundamental researches into the causation of the different forms of this disease. Tularemia, a disease discovered by the U. S. Public Health Service, has been discussed under the supervision of Dr. Francis of that Service. The chapter on rabies has been read in part by Lieut.-Colonel James G. Cumming, whose discovery of a modified treat-

ment of this disease has received general recognition. In the preparation of our article on botulism we are indebted for valuable suggestions to Professor W. D. Bigelow, Scientific Director of the Laboratories of the National Canners Association. Professor Meyer, of the University of California, and Dr. Geiger, of the U. S. Public Health Service, have permitted us to read and to utilize materials contained in papers on botulism which they have prepared but have not yet published. To all these gentlemen our thanks are herewith tendered. The illustrations in this volume were prepared by Mr. Harold Corsett, of the Engineering Section of the Detroit Department of Health. With the kind permission of the International Board of Health we have utilized some of their charts.

CHAPTER II

ACCESSORY FOOD FACTORS

VITAMINS

Discussion.—Some thirty years or more ago it seemed that the chemist had solved all the problems concerning the nature and composition of our foods. He had determined the amount of water in every organ and tissue in man's body; had estimated the amount of moisture in our foods; had calculated the quantity of fluid that the average man should consume each day; had determined the amount of water leaving the body daily through the kidneys, bowels, skin, and lungs. He had made both qualitative and quantitative determinations of the inorganic constituents of bone, muscle, and brain; had estimated the amount of each of these substances in our foods and had shown how they are absorbed and assimilated. He had proved that all carbohydrates, so far as they serve as foods, are converted into sugars in the alimentary tract, absorbed through the hepatic circulation, deposited in the liver as glycogens, again converted into sugar and distributed through the body at need; again deposited in muscle and other tissue as glycogen, and finally burned into carbonic acid and water, thus supplying the animal machine with energy. He had broken up the neutral fats into glycerin and fatty acids; had shown how a like process is accomplished in digestion; how the digested fats are absorbed, distributed through the body, and finally burned, with a further supply of energy. He had taken the proteins of our tissues and of our foods to pieces; had shown that the proteins are composed of amino acids; had determined the amount of amino acid in the various proteins of the human body and calculated the daily supply of amino acid needed to keep the body in health. He had constructed long tables showing the percentages of water, inorganic salts, carbohydrates, fats, and proteins in foods. He had calculated the amount of each food principle essential to the daily diet in order to supply the machine with sufficient energy to enable it to accomplish its work, and with sufficient constructive material to repair any wear and waste in the machine itself. He had determined that our daily diet should consist of so much water, so much and certain kinds of inorganic salts, so much carbohydrate, fat, and protein. He believed one carbohydrate to be as good as another, provided the two were equal in energy content; that one fat could supplant another in our food, provided that in the exchange quantity should be considered; that proteins consist of amino acids and each of these must be present in at least the minimum amount necessary to build

up the proteins of the human body. He emphasized the necessity of being in a state of nitrogen equilibrium, with the amount of each element equal in the ingesta and the egesta. All these things and more, the chemist, as we have said, had done thirty years or more ago. What was there remaining for him to do? He had made it possible, apparently, to calculate the kind and amount of food principle daily necessary in the ingesta according to the age, weight, condition, and activities of the individual; in short, he believed that he had actually figured out our food needs, so far as amount and variety are concerned, quite as accurately as had been done for the fuel necessary to run a steam engine carrying a given load. It is true that the chemist had read the writings of Lind and others concerning scurvy, and possibly had gone through the uninteresting details of Malcolmson and others concerning beriberi, but he probably regarded these as matters of but little importance. The next thing that he attempted to do was to put together his purified food principles, seeing that each was in perfect condition and composition, and try the feeding of animals with these substances. He took purified mineral salts, carbohydrate, fats, and protein in proper amount and tried the feeding of this mixture to animals. Strange to say, he found that his animals did not live on these purified food principles, although both in quality and in quantity there was nothing wanting in either; in other words, the chemist learned that there is something more than the five food principles necessary in order to maintain the health and preserve the life of his experimental animals. For a while, he thought that there might be a deficiency in one or more amino acids in his purified protein, and, when this was found to be the case, he supplied the lacking amino constituent. Purified gliadin, one of the wheat proteins, was found insufficient when mixed with other food principles to support life, but gliadin is known to be wanting in one amino acid, lysin. This was prepared and added to the purified gliadin. With this addition, this protein was mixed with mineral salts, carbohydrates, and fats, and still it was found that animals fed on the preparation did not do well. The chemist then recalled the experiments of Eykman and others in the production and cure of polyneuritis in birds and the application of this principle to the treatment of beriberi in man. As early as 1906 Hopkins, after failure to keep animals in health on purified protein, carbohydrates, and fats, recognized the fact that besides these there are certain other essential constituents of the diet and he proposed that they should be called "accessory food factors." At that time Hopkins wrote:

"But, further, no animal can live upon a mixture of pure protein, fat and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal body is adjusted to live either upon plant tissues or the tissues of other animals, and these contain countless substances other

than the proteins, carbohydrates, and fats. Physiological evolution, I believe, has made some of these well-nigh as essential as are the basal constituents of diet; lecithin, for instance, has been repeatedly shown to have a marked influence upon nutrition, and this just happens to be something already familiar, and a substance that happens to have been tried. The field is almost unexplored; only is it certain that there are many minor factors in all diets, of which the body takes account. In diseases such as rickets, and particularly in scurvy, we have had for long years knowledge of a dietetic factor; but though we know how to benefit these conditions empirically, the scale errors in the diet are to this day quite obscure. They are, however, certainly of the kind which comprises these minimal qualitative factors that I am considering. Scurvy and rickets are conditions so severe that they force themselves upon our attention, but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors."

Since that time many investigators have engaged in attempts to acquire some knowledge of these mysterious bodies. Funk, who has contributed much of value along this line, seems to have been dissatisfied with the designation of them chosen by Hopkins and proposed that they be called *vitamines*. This term, like many others selected prematurely by scientific investigators, has turned out, with our increasing knowledge, to be quite unsatisfactory. The prefix, *vita*, would indicate that these substances are essential to health and life. While this is true, it is equally true of any one or of all of the five food principles. The second part of the word, *amine*, had already had a specific meaning in chemical nomenclature, in which an amine is a compound formed by the substitution of an organic radical for one or more of the hydrogen atoms in ammonia. There is no reason for believing that any one of the accessory food factors is an amine in the chemical sense. The reader must, therefore, bear in mind that the word "vitamine" is inappropriate in this connection and we use it, notwithstanding the objections we have urged against it, because it has become fixed in medical and scientific literature. McCollum, after registering his protest against the term vitamin, designates the accessory food factors by their solubility, as fat-soluble A and water-soluble B, but, as some one has pointed out, there is objection to this, because solubility depends upon the absence or presence of other substances. Moreover, the water-soluble B is also soluble in at least ninety per cent alcohol and the fat-soluble A has been reported as extractable from fats by means of water. It has been suggested that in order to avoid the confusion of the term *vitamine* with the amines spoken of by organic chemists we write the word without the final "e", but this is frequently done by the organic chemist.

We shall begin our discussion of the accessory food factors with the work of McCollum and his colleagues, notwithstanding the fact that in point of time there were important contributions to this subject before McCollum began his researches. This talented investigator, working at

the Wisconsin Experiment Station, took four groups of heifers, weighing about 300 pounds each. Each group was kept separately, properly stabled and allowed the run of an open lot free from vegetation. The sole food of the first group consisted of the wheat plant, the grain, straw, and the addition of wheat gluten; the second group was confined to the corn plant and its products, including grain, corn gluten, leaves, and stalks. The third group had only rolled oats and oat straw, while the fourth group, intended to serve as controls, was fed about equal parts of wheat, corn and oat products. All the animals in these groups were watered from the same supply and had common salt *ad libitum*. All ate about the same amount, apparently digesting it, and suffered from no recognized disease. After one year on these diets the members of the corn-fed group were sleek, fine, and apparently in an excellent state of nutrition. The members of the wheat-fed group were rough coated, gaunt, and of small girth. The weights of the two groups did not differ materially. The members of the oat-fed group and of those fed upon the mixed plants stood intermediate between the corn and wheat lots. The corn-fed animals were in every way better off, at least of better appearance, than the members of any other group. In due course of time all these animals produced young. The calves of the corn-fed animals weighed at birth from 73 to 75 pounds, came at the right time, were able to stand and nurse within an hour after birth, and grew into vigorous animals. The young of the wheat-fed group averaged 46 pounds at birth, came from three to four weeks too soon, and were either born dead or died within a few hours. The young of the oat-fed animals averaged 71 pounds, came two weeks too soon, one of the four was born dead and two were weak and died within a day or two, while the fourth was weak but was kept alive with care. The young of those fed upon the mixed plants were weak, one was born dead and one lived but six days.

During the first 30 days of lactation the average production of milk per day for each animal in the corn-fed lot was 24.03 pounds; in the wheat-fed, 8.04; in the oat-fed, 19.38; in those fed on mixed plants, 19.82 pounds. The only abnormality that could be found in the excretions of these animals was that, while the urine of the other groups was neutral or alkaline as it should be, that of the wheat-fed group was distinctly acid. No explanation for this difference has been found. These animals were continued under the experiment through a second period of gestation and lactation with no material differences from those that characterized the first year. This is a very striking experiment and it suggests many problems which are as yet unsolved. It will be easily understood that the repetition of this experiment with cattle would be costly and would require many years before a satisfactory explanation could be reached. For these reasons McCollum changed his experimental investigations over to rats. The average

length of a rat's life, with proper food, is about 36 months. The female has her first litter at about 120 days and, as a rule, has five litters by the time she reaches the period of sterility, which is 14 months. The period of gestation is 21 days and the young are ready to wean at the age of 25 days. These qualifications render this animal highly suitable for nutritional experiments. McCollum found that when he fed batches of rats upon what he supposed to be purified food principles, the daily diet consisting of 18 per cent purified casein, 20 per cent supposedly pure lactose, about 5 per cent of some fat, with the proper mineral addition and the remainder of starch, the animals thrived whenever the fat in the mixture was butter-fat but failed when butter-fat was replaced by lard, olive oil, or other vegetable oils. The butter-fat could be supplanted by fat obtained from egg yolks and from certain other animal sources. This experiment, repeated many times, shows that butter-fat contains something which is not found in vegetable fats and that the latter cannot be substituted for the former. There is, therefore, in butter an accessory food factor, and McCollum has designated this as fat-soluble A. This experiment has been repeated so often, with so many modifications and by so many investigators, that the existence of fat-soluble A may be regarded as having been established.

In other experiments, McCollum and his colleagues found that when thoroughly purified lactose or milk sugar was used in his rat dietary, the animals did not thrive even when butter-fat was a constituent of their food. This indicated that the impure milk sugar contains some substance essential to growth, the character of which is unknown. Subsequent investigations have shown that this is a second accessory food factor and it is now designated as water-soluble B. The fat-soluble A is found in butter, certain other animal fats, and in the leafy parts of plants. The water-soluble B is widely distributed in nature and is now recognized as the antiberiberic vitamin.

Independently of McCollum, and indeed prior to his publications, Hopkins, in England, had found experimentally that, while animals fed upon purified protein, carbohydrate, fats, and mineral salts, did not grow and, indeed, did not maintain body weight, they did thrive when to the above-given diet there was added enough milk to supply four per cent of the total dry matter of the food mixture. Stepp found that mice thrive satisfactorily when fed on bread made with milk; that the residue left after extracting this bread with alcohol did not support the mice, but returning to the bread the substance extracted with the alcohol, rendered it a satisfactory food. In view of McCollum's work, the explanation of this is that the fat-soluble A in the bread and due to the milk was extracted from the bread with the alcohol.

It should be clearly understood that fat-soluble A and water-soluble B

are different and distinct substances and that one of these in the food does not do away with the necessity for the presence of the other. The addition of butter-fat or fat-soluble A to polished rice does not prevent the development of polyneuritis in birds or of beriberi in man, nor will such a food cure these diseases.

McCollum says:

“(1) Seed mixtures, no matter how complex, or from what seeds they are derived, will never induce optimum nutrition. Seeds with tubers, or seeds with tubers, roots, and meat (muscle) will in all cases fail to even approximate the optimum in the nutrition of an animal during growth. (2) The only successful combinations of natural foods or milled products for the nutrition of an animal are (a) combinations of seeds, of other milled products, tubers and roots, either singly or collectively taken with sufficient amounts of the leaves of plants; (b) combinations of the foodstuffs enumerated under (a) taken along with a sufficient amount of milk to make good their deficiencies. *Milk and the leaves of plants are to be regarded as protective foods and should never be omitted from the diet. Milk is a better protective food than are the leaves, when used in appropriate amounts.*”

According to McCollum, meats (muscle) compare in their dietary properties more closely with the seed than with the leaf, only that the protein in meat is of much higher biologic value than that in seeds. The glandular organs, the liver, kidneys, thyroid, spleen, etc., are richer in both fat-soluble A and water-soluble B than is muscle, although the glandular organs mentioned contain certain substances which are so highly active that too much of them or too long continuance of their use in large quantity might do harm. The yolk of eggs is also rich in fat-soluble A and water-soluble B, but, of course, it will be understood that eggs are deficient in carbohydrates and in mineral constituents and these deficiencies should be made good by the addition of other foods to the diet. Fat-soluble A is apparently quite resistant to high temperature and to subjection to other processes employed in the preparation and preservation of food. Osborne and Mendel state that passing of steam through melted butter for two hours has no deteriorating influence upon its growth-promoting properties. Butter in evaporated milk seems to be quite as effective as that in the freshly drawn fluid. There can, therefore, be no serious objection from this standpoint to the use of canned milk or dried milk powder. A like persistence of fat-soluble A is evident in the examination of dried leaves. Alfalfa leaves may be dried, ground into powder, and kept indefinitely, so far as investigations up to the present time go, without material loss in their content of fat-soluble A. McCollum states that celery tops may be dried in the sun or by artificial heat in a current of air, with preliminary treatment with steam, without loss in the fat-soluble A constituent.

McCollum is quite positive that there are only two accessory food factors,

and these are fat-soluble A and water-soluble B. He is so certain of this that he makes the following statement in italics:

"It is now well demonstrated that with the diets employed in Europe and America there is no such thing as a 'vitamine' problem other than that of securing an adequate amount of the substance, fat-soluble A."

We suppose that in making this statement the author does not include Brazil and Newfoundland in America, because the existence of beriberi in these parts of South and North America is now well recognized.

Xerophthalmia. McCollum and his colleagues have found that when rats are fed upon a diet deficient in fat-soluble A the eyes swell badly and are opened not at all or with difficulty. The cornea becomes inflamed and if fat-soluble A is not added to the diet, blindness speedily results. A like condition had been previously observed by Osborne and Mendel and they also found that it is relieved by the addition of butter-fat to the food. With 5 per cent or more of this substance added, prompt recovery follows within two weeks if the sight has not been destroyed, and even after the sight has been destroyed the lids may be restored to the normal condition by the addition of butter fat. In 1904 Mori reported 1,400 cases of xerophthalmia among children in Japan at a time of food scarcity. He reports a condition of the eyes which agrees closely with that observed by McCollum and his colleagues in animals. Mori found, and it will be understood that this observation was made before McCollum's work was done, that the disease among children was cured, or at least greatly improved, by feeding with chicken livers. In Japan, dairy products are but little employed and their principal sources of fat-soluble A lie in their leafy vegetables and their eggs, the former of which they consume in larger quantities than is done either in Europe or America. It was Mori's opinion that the xerophthalmia which he observed was due to fat starvation. The disease was not seen among those who lived largely on fish. More recently, xerophthalmia, with ulceration of the cornea, has been reported by Bloch in about 40 cases in the vicinity of Copenhagen. The food of these children had been skimmed milk and they were anemic and greatly wasted. Bloch believed the disease of the eye to be due to fat starvation and he found that infants recovered promptly when fed breast milk and older ones when given whole milk and cod liver oil. Czerny and Keller reported a similar condition of the eyes in children in Leipsic and they attributed it to restriction to a cereal diet. According to McCollum, xerophthalmia and beriberi are the only diseases which can in any proper sense be classed as deficiency diseases, the former being due to the absence of fat-soluble A and the latter to the absence of water-soluble B from the diet. While xerophthalmia may be the only disease caused by the absence of fat-soluble A and while beriberi may be the only disease caused by the absence of water-soluble B, deficiencies in the food in either or both of

these factors interfere with growth in the young and reduce the efficiency of the adult. In their earlier experiments Osborne and Mendel were able to keep full-grown rats for a short time in apparent health and in a state of nitrogen equilibrium on purified food principles, provided that the protein contained all the essential amino acids. Long continuance on this diet affected the health of adults and on it young animals failed to grow normally. The same investigators found that the growth of young animals, arrested under the restricted diet, was awakened into fresh activity by the addition of what they at that time designated as "protein free milk." This preparation was made by coagulating skimmed milk, drying the coagulum and reducing it to a fine powder. With our present knowledge we are justified in assuming that the powder thus obtained contained at least traces of both fat-soluble A and water-soluble B.

The relation of nutrition to diseases of the eyes has in late years concerned a number of observers and investigators. So far as our reading goes, Mori, whom we have already mentioned, was the first to call attention to the influence of a diet poor in milk fat upon the production of suppurative diseases of the eyes in children. In 1906 Faltz and Noeggerath, in feeding rats upon mixtures of casein, lard, starch, and dextrose, observed that at the beginning of the fourth week on such a diet many animals developed a conjunctivitis which remained incurable so long as this diet was persisted in. In 1908 Knapp repeated these observations, observed that in many animals ulcers formed on the cornea, and obtained from these lesions bacteria, mostly staphylococci. It seems that Knapp was impressed with the fact that these eye diseases were not due to starvation, but were due to the absence from the food of certain factors. He wrote as follows:

"It was not alone the premortal loss of resistance which predisposed these animals to these catarrhal inflammations, but an additional etiologic factor must be sought for in the diet, perhaps, a lack of an important element. Whether this is the case, and the nature of this element or substance, is a question which, on the basis of my investigations, I am unable to answer. Other carefully conducted experimental investigations are needed before a solution of the problem will be found."

In 1915 Freise, Goldschmidt and Frank studied the ophthalmias which frequently follow unbalanced nutrition and came to the conclusion that these diseases were due solely to infection and that the food deficiency was not concerned in their etiology. More recently, Bulley came to the conclusion, after a series of experiments that ophthalmias do not follow necessarily food deficiency and may be wholly obviated under such condition if infection is prevented. These findings by Freise and his colleagues and by Bulley have been contradicted by numerous observers, all of whom conclude that the investigations carried out by those just mentioned failed to develop ophthalmias because the food used had not been thoroughly deprived of the fat soluble vitamin. Stephenson and Clark, from the same

laboratory in which Bulley worked, found that 28 per cent of their rats kept on a diet deficient in the fat-soluble vitamin developed ophthalmia and every case was cured by the administration of this vitamin. Emmett induced xerophthalmia in 120 out of 122 rats kept on a diet from which the fat-soluble vitamin had been removed. Osborne and Mendel make the following report on 1,000 rats in their laboratories under different forms of feeding: Of 136 fed upon diets deficient in the fat-soluble vitamin, 69 developed ophthalmia; of 225 fed upon diets deficient in the water-soluble vitamin, of 90 fed upon diets otherwise deficient, of 201 fed upon adequate diets, and of 348 fed upon ordinary mixed food, not one developed ophthalmia. Wason has reported upon a pathologic study of ophthalmias developed in the laboratory of Osborne and Mendel, and states her conclusions as follows:

“(1) The primary etiologic factor in the ophthalmia of rats on deficient diets is the lack of fat-soluble vitamin A. (2) The nature and mechanism of the change in these rats whereby their corneas are rendered susceptible to bacterial invasion is unknown. (3) The type and virulence of the organisms of secondary invasion determine, in part at least, the course of the disease. (4) The anatomic manifestations of the disease are characterized by hyalinization or necrosis of the outer layer of corneal epithelium, exudation of serum and cells into epithelium and stroma, and a proliferation of blood vessels and fibroblasts. In advanced cases invasion of the anterior, and occasionally of the posterior chamber, results. (5) The degree to which restoration is possible depends upon the extent of the secondary injury.”

Cramer, Drew and Mottram report that a food deficiency in vitamins specifically and seriously affects the lymphoid tissue, causing marked atrophy in these structures. This statement needs confirmation, since it is not probable that the same tissue is affected in all deficiency diseases; indeed, we are quite sure that this is not true.

Selection of Foods.—It must be evident from what has been said, that foods should be so selected and so mixed that not only each of the five food principles is present in sufficient amount, but each of the vitamins must also be present. The best food for herbivorous animals is that which contains both seeds and leaves. There is certainly no mammal which can live and maintain its health for any great length of time when its only food supply consists of grain, tubers, or roots, any one of these or all mixed. The herbivorous animal must have a mixture of grain, or seeds and leaves. Omnivorous animals, at least some of them, may be kept alive and in fair condition on vegetable foods alone, provided both the seeds and leaves are present in the food. McCollum and his colleagues fed rats through four generations with no apparent diminution in vitality on a food mixture consisting of 50 per cent maize, 30 per cent dry alfalfa leaf, and 20 per cent cooked peas, subsequently dried. As a rule, however, the omnivorous animal does better upon a mixture of vegetable and animal food. McCollum showed that hogs retain in their bodies for growth purposes 20

per cent of the protein in the corn they eat and 63 per cent of the protein in the milk they drink. The scientific farmer has long since learned that his pigs do not do best when their food is confined to grain. In some quarters we hear much about the danger of eating too much animal food, and the deadly poisons which these foods are supposed to contain are accredited with many of the ills to which flesh is heir. The so-called vegetarian as a rule adds eggs and milk to his daily diet. Eggs and milk are quite as distinctly of animal origin as are beef and pork. There can be no question that an unobjectionable dietary can be secured by the employment of vegetables, milk, and eggs. Some years ago Slonaker took two groups of young rats. To one group he supplied daily *ad libitum* 23 vegetable foods. This group was not given any animal food. The second group had the same vegetable foods and in addition thereto, small quantities of animal food. The vegetarian group did well for a time but never passed beyond 60 per cent of the normal adult size. The average length of life in this group was 555 days. The omnivorous group grew to full normal size and the average life was 1,020 days; in other words, the vegetarians grew to a little more than one-half the adult size and lived a little more than one-half the average life. Anatomically man is not so constructed that he can eat large quantities of leaves and herbs, and a study of the vitamins shows that in order to grow normally, reach proper maturity, do his work satisfactorily, and reproduce his kind in a worthy way, man must exercise some care not only in the selection, but in the preparation, of the foods he eats. We are not alarmed with the fear that scurvy or beriberi is likely to become an important factor in the deterioration of the people of the United States, but we do claim that these people would be stronger, freer from disease, and more nearly correct in their mental and moral attitudes if they selected their foods more wisely. At the present time we are not under the necessity of going to Vienna or Prague in order to see undernourished children. They are numbered by the thousands in our large cities and it is not difficult to find them in our villages and even on our farms. Undernourishment and its accompaniments are to be seen not only in the children of the poor, but in the homes of the well-to-do and the rich. The belief that instinct and desire lead every feeding animal, and especially man, to choose what is best for him is erroneous. The young men drafted from the pellagrous districts in our southern states and sent to camp, for a time rebelled at the kind of food supplied them in their mess tents, although this was more abundant, more varied, and more nutritious than any they had ever seen. They had been brought up on hominy or corn grits, corn-bread, molasses, tea and coffee, and they sat at the abundantly supplied tables in the camps and sighed for their home food. Taste for food is a matter of education and habit and in this, as in other directions, bad habits are easily acquired and long continued. Many of the studies in food consumption

that have been made are not only worthless, but they are grossly misleading. Because a thousand, more or less, people living in a certain community buy and consume an abundant supply of food is by no means proof that each individual in that community gets or chooses the proper food either in quality or quantity. We may go further and say that because a family of seven or eight buys so many eggs, so much meat, so much milk, etc., weekly or daily, does not prove there are not in that family one or more individuals who fail to get proper food. Before any positive and trustworthy conclusions can be drawn concerning the effects of different foods on children, we must know that each child gets his proper proportion or selects the food that is best for him. Fortunately, the nutrition of children in this country is now coming under the observation and study of the physicians of the health departments of our cities, and we predict that when the data have been accumulated through a few years it will be shown that even here in this rich and prosperous country and even in the homes of the well-to-do and rich, there are children who are suffering because they are eating insufficient, unbalanced, badly prepared food. All through the papers on experimental scurvy and beriberi that we have read we are impressed with the fact that these are not starvation diseases, but that they result from the consumption of foods either unsuited by nature or changed in their preparation for the table. In many of the experiments in the production of beriberi it is shown that the disease is more promptly and more severely developed with increased amount of carbohydrate fed. The enormous quantities of candy and sugar in other forms consumed by our children increase the amount of antiberiberic vitamin that their other foods must contain in order to keep them from developing distinctive symptoms of beriberi. The children of the well-to-do and many of those of the poor eat too much carbohydrate and drink too little of good rich milk. This is true in the city, in the village, and on the farm. Coffee or tea takes the place of milk in the early years of life; white bread has practically driven the whole-wheat products from the market; sweets which contain no vitamin of any kind are consumed in large quantities, ferment in the alimentary canal, encourage the growth of bacteria, destroy all desire for vitamin containing food; growth is arrested in the young and the degree of invalidism among adults is increased.

The physician should take a broad view of nutritional disorders and he should not wait until scurvy, beriberi or pellagra has developed before he makes special inquiry into the dietaries of his patients. In this connection, we make the following quotation from Hess:

“The current view associates deficiencies of the various vitamins with specific disorders, for example, with beriberi or with scurvy. Now, although it is quite true that such diseases demonstrate conclusively the absolute necessity of certain constituents in our dietary, it is likewise true that clear-cut disorders should not be re-

garded as the most common or important result of food deficiencies. It should be realized that a lack of these essential food factors generally does not bring about typical pathologic states, but obscure alterations of nutrition, ill defined functional disabilities, which cannot be characterized or even recognized as disease. It is such incomplete, larval forms of the deficiency disorders to which physicians will have to address themselves. Nor should the domain of the deficiency disease be restricted to the narrow confines of disturbances brought about by a lack of vitamins. In a broader sense it includes malnutrition due to an insufficiency of any food constituent which is essential to normal metabolism. The peoples of the Central Empires, for example, as the result of a great lack of meat, milk, cheese and eggs, were compelled to subsist during the war on a dietary which was deficient in phosphoric acid as well as in one or more of the vitamins. Many observations lead to the conclusion that these disorders are not limited to man, but to a large extent affect the animals which man uses for food. It has been found in Victoria, for example, that cattle raised on certain pastures develop paralysis and other infirmities which can be cured by fertilization of the soil. In the United States in some areas it is impossible to maintain cattle in good condition until the forage is improved by mineral or animal fertilizers, which illustrates that a deficiency in plant tissues leads to nutritional disorder in animals. Recently Hart, Steenbock and Humphrey have confirmed these observations by careful experiments which showed how the mere addition of calcium to the fodder of cows prevented the birth of premature, weak or dead calves. Indeed, the extensive investigations of Forbes showing that cows producing large amounts of milk, and fed common winter rations, undergo constant losses of calcium, magnesium and phosphorus from their skeletons, suggest that large numbers of milch cows are suffering from a deficiency disease. These chemical analyses recall Hanau's report of almost thirty years ago, to the effect that the bones of pregnant women, who had enjoyed apparent health, frequently were the site of lesions resembling osteomalacia—an interesting observation that might be substantiated during life by means of roentgenologic examinations."

Soon after the armistice, English physicians, armed with all known means of combating the deficiency diseases, hastened to Vienna, Prague, Berlin, and other capitals of their recent enemies and offered their aid to the famine stricken people. From the staff of the Lister Institute there has come a statement of what is known or supposed to be known of practical benefit in the treatment of these diseases. From this statement we make a brief abstract, which is as follows: The accessory food factors now recognized are three in number. The antineuritic or antiberiberic factor, the same as water-soluble B, prevents the occurrence of beriberi in man and analogous diseases in animals. Its presence in the food is also necessary to promote satisfactory growth in the young. This vitamin is distributed and is present to some extent in almost all natural foods. Its principal sources are in eggs and in the outer layers of seeds. Meat (muscle) contains but little of this antineuritic factor, but it is abundant in highly cellular organs, such as the liver, brain, pancreas, etc. In peas, beans, and other pulses, this vitamin is distributed throughout the seed, but in cereals it is concentrated in the peripheral layer, which in milling is peeled off with the pericarp and forms the bran. Beriberi is occasioned by a diet

composed too exclusively of cereals from which the bran has been removed by milling, as is the case with polished rice or white wheat flour. The disease is unknown where rye bread is the staple food, because in the milling of rye there is no separation of the germ. It is not likely that beriberi will become a serious disease in eastern Europe, notwithstanding the famine conditions, so long as whole meal flours from rye, wheat, barley, maize, peas, beans, and lentils are provided. Mere shortage of food does not cause beriberi and poverty insures that the whole grain is consumed for purposes of economy.

The second known accessory food factor is designated as fat-soluble A, growth factor, or antirachitic factor. The memorandum recites that evidence is accumulating that rickets is caused by a shortage not of fat as such, but of the fat-soluble growth factor which is contained in certain fats. Infants and young children must, therefore, be supplied with full-cream milk if possible. If fresh milk is not obtainable, condensed, unsweetened cream or milk should be used. When these foods are employed an antiscorbutic should be added. Sweetened condensed milk is unsuitable because the high content of sugar renders the food deficient in the fat-soluble factor when it is diluted sufficiently to be used. Milk and butter are the best sources of the antirachitic factor for young and growing children. Margarines made from animal fats are also valuable, but those from vegetable fats are to be condemned. If there be a shortage of butter it should be reserved for children, but if this food be totally lacking the deficiency can be replaced by cod-liver oil and other fish oils or by eggs. If no animal fat is available peanut oil should be selected in preference to other vegetable oils for the preparation of margarines, etc., and some effort should be made to utilize the fat-soluble vitamin contained in green leaves. Green leaves are a cheap and easily available source of the fat-soluble vitamin and adults can maintain health when animal fats are substituted by vegetable fats in green leaves when it is possible to consume these in sufficient quantity. Unfortunately, infants cannot take green vegetables in the ordinary way, but the juices expressed from cabbages and other green-leaf vegetables, raw, or even after steaming for a few minutes, might be given to infants if all other sources of this important vitamin have failed. Carefully prepared purées from cooked spinach or lettuce can be tolerated by infants in small quantities, as one teaspoonful daily. In cases where growth failure, rickets, or xerophthalmia are already well established, a daily dose of cod-liver oil is essential in addition to other procedures. Pregnant women and nursing mothers should have a liberal supply of fat-soluble A and it should be understood that rickets is not confined exclusively to artificially fed children. Breast-fed children may develop it, provided the vitamin is deficient in the milk of the mother.

The third factor, the antiscorbutic factor, necessary for the prevention

of scurvy, is found in fresh vegetable tissue, to a less extent in fresh animal tissue. Its richest sources are oranges, lemons, raspberries, cabbages, swedes, turnips, lettuce, watercress, and tomatoes. Potatoes, carrots, beet roots, and mangolds are inferior in this vitamin to the sources named above. It should be understood, however, that potatoes are valuable in the prevention of scurvy, notwithstanding their small content of the antiscorbutic vitamin, because they are consumed in large quantities. All dry foodstuffs are deficient in antiscorbutic properties, such as cereals, pulses, dried vegetables and dried milk. Tinned vegetables and tinned meat are also deficient in the antiscorbutic principle. It is claimed by some that canned tomatoes are valuable for their antiscorbutic properties. In case fresh vegetables or fruits are scarce or absent, an antiscorbutic can be prepared by moistening any available seeds (wheat, barley, rye, peas, beans, lentils) and allowing them to germinate. It is necessary that these seeds should be in the natural whole condition, not milled or split. The seeds should be soaked in water for 24 hours and kept moist with access of air from one to three days, by which time they will have sprouted. The antiscorbutic vitamin is present in the sprouts, and these should be cooked for as short a time as possible. It should be understood that salads are more valuable than many fresh vegetables, and certainly much more valuable than cooked vegetables. Cow's milk, even when raw, is not rich in the antiscorbutic vitamin; when heated, dried, or preserved, the amount contained is still further reduced. The most valuable antiscorbutic material is fresh orange juice, which should be given to children in doses of from one to three or four teaspoonfuls per day. Raw swede, if available, or turnip juice, is a potent antiscorbutic and an excellent substitute for orange juice. In order to obtain this juice the clean-cut surface is grated on an ordinary kitchen grater and the pulp obtained is squeezed through muslin. Tomato juice, even that from canned tomatoes, and grape juice, also have some value, but less than that of orange. When babies have scurvy or neuritis the mother should have in her food both antiscorbutic and anti-beriberic vitamins. Reports that come from Vienna and other southeastern European capitals where these principles have been applied since the armistice, indicate that great good is being done, and we have no doubt that the intelligent physicians who are making these applications will greatly advance our knowledge of the vitamins by their studies and observations.

Recently (1921) McCarrison has published a monograph filled with the protocols of numerous experiments, especially upon pigeons and monkeys, in which one or more of the vitamins have been omitted. The most valuable part of this work lies in the pathologic studies, in which it is shown that when one or more vitamins are absent from the diet pathologic changes

begin to take place, especially in the alimentary canal and in the endocrin glands, long before the disturbances are sufficient to be clinically recognized. It is also clearly brought out in McCarrison's studies that deficiency in vitamins increases susceptibility to infection and, what is of equal importance, a properly selected diet plays a large part in the treatment of the infectious diseases. Up to the present time the study of vitamins has been largely the work of the biologic chemist. McCarrison has supplemented chemical investigations by an extensive experimental study of the symptomatology and pathology of deficiency diseases. We make the following quotation from this author's statement concerning the selection of food:

"It is agreed by all workers on the problems of nutrition that vitamin A is frequently deficient in the food; but because of the 'antineuritic' cloak under which the true function of vitamin B has so long been hidden, it is less readily agreed that this also is frequently insufficient. I admit that it is difficult to deprive a dietary of this factor; but since it is not known how much of it is needed for perfect nutrition in human beings, it is best to err on the safe side; and to see that in all cases the food contains plenty of it. Nature gives us a fair hint as to its necessity; for we find it in abundance in the natural foodstuffs which man ought to eat and frequently does not. It requires little laboratory experimentation, therefore, to show that some people, especially the young, habitually take too little of it, either for growth or maintenance.

"As for vitamin C, we are accustomed to recognize its insufficient supply only when the gums begin to bleed or the tissues begin to show signs of hemorrhagic effusions. But the evidence brought forward in preceding chapters indicates that, long before these grosser evidences of insufficiency manifest themselves, the health of the gastrointestinal tract and of the adrenal glands has begun to suffer. It is not enough, then, that the supply of vitamin C should be sufficient to prevent scurvy; it should be sufficient to play adequately its part in maintaining the digestive and endocrin organs in health; this sufficiency can only be secured by the inclusion in the dietary of an abundance of raw fruit and vegetables. There are no more important ingredients of a properly constituted food than these, since they contain vitamins of every class, recognized or unrecognized.

"In the selection of foods, or in estimating the value of a patient's diet, it is sufficient in practice to see that he receives an adequate supply of natural protective food ingredients. It is hardly necessary to emphasize that these natural foods must be used in a form which does not depreciate their vitamin value, and in a form suitable to the age and state of digestion of the individual. Thus in infants and young children, fruit and vegetable juices will be used instead of the whole product; while such articles as whole-meal, bread and nuts will be presented only to gastrointestinal tracts capable of dealing with them. Similarly, in cases of gastrointestinal disorder, vitamin-containing extracts or fruits and vegetable juices may alone be tolerated until the tract has had time to recover in some measure its normal tone and digestive powers. Nor is it necessary to abandon foods in common use; all that is required is to reinforce these with natural foodstuffs in quantities sufficient to provide an adequate supply of vitamins, suitable protein, and salts for the varying needs of individuals."

Bibliography

- HOPKINS, F. G.: Jour. Physiol., 1912, xlv, 425.
- McCARRISON, R.: Studies in Deficiency Diseases, London, 1921, Henry Frowde & Hodder & Stoughton.
- McCOLLUM, E. V.: The Newer Knowledge of Nutrition, New York, 1910. The Macmillan Company.
- OSBORNE, T. B., AND MENDEL, L. B.: Jour. Biol. Chem., 1913, xvi, 431; *ibid.*, 1915, xx, 378; Jour. Am. Med. Assn., 1921, lxxvi, 905.
- SLONAKER, J. R.: Leland-Stanford, Jr., Univ. Publications, 1912.

CHAPTER III

SCURVY

Description.—Scurvy is a grave, nutritional disorder, which follows restriction to a diet containing too little fresh food. In certain foods, both animal and vegetable, there are substances, the nature of which is as yet unknown, but which are essential to the maintenance of health. The distribution of these substances in our foods is widely variable. Some foods are wholly devoid of these antiscorbutic principles, while the amounts present in other foods differ widely. The amount in a given food at the time of its consumption depends largely upon the time which has elapsed since the harvesting of the food and with the processes of preparation to which it has been subjected. When a diet deficient in these important constituents is continued as the sole nutritional support of an individual, sooner or later, generally within a few months, a well marked and characteristic disease, which we designate as scurvy, develops. Those in whom the symptoms and lesions of this disease have appeared are quickly restored to health, provided the delay has not been too long, on addition to the diet of foods rich in antiscorbutic principles. The chief pathologic state which develops under this deficient diet results in an abnormal permeability of the walls of the capillaries, in consequence of which serum and blood diffuse into the tissues. The effect of this pathologic condition is generally first evident in the gums. These are swollen and bleed easily, cover the teeth preventing mastication, and are often invaded by bacteria and fungi. The teeth become detached from their bony sockets and often drop out. In severe cases the mouth is filled with an abnormal growth which becomes putrid and gives off disagreeable, foul-smelling gases. Hemorrhages occur in other parts of the body, notably in the lower extremities. There are effusions under the skin, appearing in the form of petechiae, vibices, and other spots. Deeper hemorrhages lie between the muscles and give rise to swelling and pain. There may be still deeper hemorrhages, and clots may form between the bones and the periosteum. The development of these pathologic states is accompanied by general weakness, with feeble pulse and shortness of breath. Sudden death, especially on making any unusual effort, is by no means rare in scurvy. The bodily resistance to infection is lowered and bacteria often play a part in the final stages of this disease. It should be clearly understood, however, that scurvy is not an infectious disease, but is due wholly to nutritional disorder.

History.—Some have attempted to find in the writings of Hippocrates evidence that this disease was known to Greek medicine. The arguments adduced for this view are by no means convincing and it is highly improbable that scurvy existed during either the Greek or Roman periods of Mediterranean civilization. The soil and climate of these regions furnished man with a variety of food, much of which was consumed soon after being gathered. Although food may have been scanty at times, especially in war, it was always present in variety and man had not at that time learned the art of storing and preserving his food-supplies. There were no long voyages and man lived more directly from hand to mouth than his fellow did, even at that time, in the colder parts of northern Europe. The word scurvy is from the old Saxon “scorbie” and this occurs with some modification in all the tongues of central and northern Europe. It is highly probable that scurvy afflicted our Nordic ancestors even at as early a date as the time of Hippocrates, but our fathers of that time were not writing books or at all concerned with making records for our enlightenment.

Budd says:

“Scurvy has, unquestionably, existed in the north of Europe from the most remote antiquity. That we have no mention of it in the early history of the northern nations must be imputed to the extreme ignorance of the people, especially as regards medicine; but about the commencement of the sixteenth century, when they began to cultivate letters, we find accurate description of this disease, which is frequently mentioned by their historians and other authors. Olaus Magnus in his *History of the Northern Nations*, published in 1555, when speaking of the diseases peculiar to those nations, gives a particular description of scurvy, which, he tells us, infested chiefly soldiers in camps and persons shut up in prisons or besieged towns. About the same time we find three physicians, Ronseus, Eethius and Wierus, expressly treating of this disease. Their descriptions of its symptoms are very accurate, and they recommended those remedies which are found, at present, the most efficacious.”

The first clear and indisputable record of scurvy is to be found in the *History of Louis IX and His Crusaders*, by Joinville (1260). This historian not only saw the disease, but he himself had it. In speaking of the condition of the gums, he says:

“The barbers were forced to cut away large pieces of flesh from the gums, to enable their patients to eat. It was pitiful to hear the cries and groans of those on whom this operation was performing; they seemed like the cries of women in labor.”

This disease fell upon the crusaders in lent when, on account of their religion, they could eat no meat and were confined so far as flesh is concerned to one sort of fish, the bombette.

As soon as long voyages by sea were attempted, scurvy among sailors began to be reported. In 1497 Vasco da Gama made the first trip around the Cape of Good Hope to India and the chronicler of this voyage says that his sailors suffered severely from scurvy.

“Of an hundred forty-eight, or as others report, of an hundred and three score, there returned only five and fifty, and those very feeble.”

In 1519 Magellan started upon his voyage around the world, leaving Seville on the tenth of August. After leaving the straits which still bear his name, and standing out into the Pacific Ocean, his men were seriously stricken by this disease. Pigafetta, the historian of this voyage, writes as follows:

“Departing out of this strait into the sea called Mare Pacificum, the eighth and twentieth day of November, in the year 1520, they sailed three months and twenty days before they saw land; and having in this time consumed all their biscuit and other victuals, they fell into such necessity, that they were enforced to eat the powder that remained thereof, being now full of worms and stinking, by reason of the salt water. Their fresh water was also putrefied and became yellow. They did eat skins and pieces of leather, which were folded about certain great ropes of the ships; but these skins being made very hard, by reason of the sun, rain and wind, they hung them by a cord in the sea, for the space of four or five days to soften them and then they ate them. By reason of this famine and unclean feeding, some of their gums grew so over their teeth, that they died miserably for hunger. And by this occasion died nineteen men, and also the giant, with an Indian of the land of Brazil, otherwise called Terra de Papagilli, that is the Land of Poppingayes. Besides these that died five and twenty or thirty were so sick, that they were not able to do any service with their hands or arms for feebleness; so that there was in manner none without some disease.”

The following unmistakable and graphic description of scurvy is taken from an account of the second voyage of Cartier to Canada in 1535:

“In the month of December, we understood that the pestilence was come upon the people of Stadacona; and in such sort, that before we knew of it, above fifty of them died. Whereupon we charged them neither to come near our forts, nor about our ships. Notwithstanding which, the said unknown sickness began to spread itself among us, after the strangest sort that ever was either heard of or seen; inso-much that some did lose all their strength; and could not stand upon their feet; then did their legs swell, their sinews shrunk, and became as black as a coal. Others had also their skin spotted, with spots of blood, of a purple color. It ascended up their ankles, knees, thighs, shoulders, arms, and neck. Their mouth became stinking; their gums so rotten, that all the flesh came away, even to the roots of their teeth; which last did also almost all fall out. This infection spread so about the middle of February, that of a hundred and ten people, there were not ten whole; so that one could not help the other; a most horrible and pitiful case! Eight were already dead; and more than fifty sick, seemingly past all hopes of recovery. This malady being unknown to us, the body of one of our men was opened, to see if by any means possible the occasion of it might be discovered, and the rest of us preserved. But in such sort did the calamity increase, that there were not now above three sound men left. Twenty-five of our best men died; and all the rest were so ill, that we thought they would never recover again; when it pleased God to cast his pitiful eye upon us, and send us the knowledge of a remedy for our health and recovery.

“Our captain considering the deplorable condition of his people, one day went out of the fort, and walking upon the ice, he saw a troop of people coming from Stadacona. Among those was Domagaia, who not above ten or twelve days before

labored under this disease; having his knees swelled as big as a child's head of two years old, his sinews shrunk, his teeth spoiled, and his gums rotten and stinking. The captain, upon now seeing him whole and sound, was thereat marvelous glad, hoping to know of him how he had cured himself. He acquainted him that he had taken the juice of the leaves of a certain tree, a singular remedy in this disease. The tree in their language is called *amedá* or *hannedá*; by a decoction of the bark and leaves of which, they were all perfectly recovered in a short time."

This tree has been identified as a spruce.

Subsequent voyages to Canada, made by both French and English, met with like experiences and during the final contest between these great nations for the permanent possession of Canada both armies, including our colonial aides with the English, suffered greatly from scurvy.

The first work on scurvy by a physician was published at Cologne in 1541. The author, a Hollander, latinized his name, making it Eethius. Among the certain signs, he enumerates a fetid breath, a spongy swelling of the gums, which are apt to bleed, a loosening of the teeth, the appearance of livid spots on the legs and sometimes on other parts of the body, and a weakness which follows these developments, often terminating in sudden death.

In 1564 Ronsseus wrote an excellent monograph on scurvy and it appears that this passed through two or more editions rather speedily. This author states that at the time of writing, scurvy was common in Holland and he attributed it to the food and air. For treatment he relied upon a diet of fresh vegetables, employing generally scurvy grass, watercresses, and infusions of various green herbs and plants. In this book there appears, so far as we know, the first recommendation of oranges in the treatment of scurvy. The author states that on long voyages sailors protected themselves against the disease or cured themselves of it by eating oranges. It seems from this that of the citrous fruits subsequently employed in the prevention and cure of scurvy, oranges were first recognized as having great value.

In 1567 Wierus, physician to the Duke of Cleves, published a monograph on scurvy. This contribution adds nothing to our knowledge of the disease except that it extends the list of plants which are useful in its prevention and cure. A favorite prescription was a decoction of saffron to be taken in a generous, warm draught three times a day. The author states that there is nothing specific in the common antiscorbutic herbs, but that all acrid plants and many roots are highly serviceable.

In 1581 Dodonaeus, physician to the Emperor of Germany, reported an epidemic of scurvy in Prussia, which he attributed to the use of spoiled rye brought from Brabant in time of scarcity of wheat. This author is the first, so far as we know, to emphasize the value of leavened wheat bread in the prevention of this disease.

In 1589 Brucaeus, a professor at Rostock, recommended a diet of well baked wheat bread, broth of flesh or fowls, with radish, hyssop, thyme,

savory, or like herbs. He also permitted flesh of all fowls except water fowls. Whatever was dried, salted, smoked, long kept and rancid, or of gross and difficult digestion, was to be avoided. Fresh milk was recommended. The antiscorbutic herbs were to be used as salads, and Rhine wine or good beer, infused with wormwood, was advised.

Albertus (1593), Professor of Medicine at Wittenburg, recommended proper diet, mentioning especially oranges, but he went astray in teaching that scurvy is contagious and may be inherited.

Forestus (1595), a professor at Leyden, became famous for a prescription which consisted of concentrated juices of brooklime and scurvy grasses. This became a popular drink throughout Flanders, Brabant, and Holland, and was used principally in the winter when green plants were not available.

Reusnerus (1600), of Norlinger, wrote voluminously about scurvy, but made no contribution of importance.

Eugalenus (1604) saw scurvy in nearly all the diseases to which human flesh is heir and in this he was, unfortunately, followed by several writers, whose names we shall not mention.

Vander Mye wrote a most graphic description of scurvy in the siege of Breda by the Spaniards in 1625. This siege lasted for eight months, terminating by surrender in June. In the preceding March it was found that 1,608 soldiers in the city had scurvy. Later, with the oncoming of spring and the appearance of plants in the besieged city, the fury of the epidemic abated somewhat. We cannot resist the temptation to make the following quotation:

“On the second day of May, 1625, when the Prince of Orange heard of their distress, and understood that the city was in danger of being delivered up to the enemy by the soldiers, he wrote letters addressed to the men, promising them the most speedy relief. These were accompanied with medicines against the scurvy, said to be of great price, but still of greater efficacy; many more were yet to be sent them. The effects of this deceit were truly astonishing! Three small vials of medicine were given to each physician, not enough for the recovery of two patients. It was publicly given out, that three or four drops were sufficient to impart a healing virtue to a gallon of liquor. We now displayed our wonder-working balsams. Nor were even the commanders let into the secret of the cheat put upon the soldiers. They flocked in crowds about us, every one soliciting that part may be reserved for their use. Cheerfulness again appears on every countenance; and a universal faith prevails in the sovereign virtues of the remedies. *The herbs now beginning to spring up above the ground, we of these make decoctions, to which wormwood and camphire were added, that by the prevalent flavor of those, they might appear medicines of no mean efficacy.* (Italics ours.) The stiff contracted limbs were anointed with wax melted in rape-seed or linseed oil. The invention of new and untried physic is boasted; and amidst a defect of every necessary and useful medicine, a strange medley of drugs was compounded. The effect, however, of the delusion was really astonishing. for many were quickly and perfectly recovered. Such as had not moved their limbs for a month before, were seen walking

the streets sound, straight, and whole. They boasted of their cure by the Prince's remedy; the motion of their joints being restored by a simple friction with oil, and the belly now of itself well performing its office, or at least with a small resistance from medicine. Many who declared they had been rendered worse by all former remedies administered, recovered in a few days to their inexpressible joy, and the no less general surprise, by their taking (almost by their having brought to them) what we affirmed to them to be their gracious Prince's cure."

Passing over a number of minor authors, it may be of interest to quote the following description of the beginnings, progress, advance, and termination of the symptoms of scurvy, as given by the great Boerhaave:

"(1) An unusual laziness; an inclination to rest; a spontaneous lassitude; a general heaviness; a pain of all the muscles as after too great a fatigue, particularly in the legs and loins; an extreme difficulty in walking, especially up or down a steep place. In the morning upon awaking the limbs and muscles feel as if wearied and bruised. (2) A difficulty of breathing, panting, and almost suffocation, upon every little motion; a swelling of the legs, often disappearing, and an inability to move them, from their weight; red, yellow or purple spots; a pale tawny color in the face; a beginning stench of the mouth; a swelling, pain, heat, and itching of the gums, which bleed upon the least pressure; bare and loose teeth; pains of different sorts wandering in all parts of the body, external as well as internal, occasioning surprising anguish, resembling pleuritic, stomacic, iliac, colic, nephritic, cystic, hepatic, and splenic pains. Hemorrhages occur in this stage, but slight. (3) A deadly stinking rottenness, inflammation, bleeding, and gangrene of the gums; loose yellow, black, and carious teeth, varicose veins under the tongue; hemorrhages, frequently mortal, from under the skin, without any apparent wound; as also from the lips, stomach, liver, lungs, spleen, pancreas, nose, etc.; ulcers of the worst kind upon every part of the body, chiefly the legs, yielding to no remedies, of a gangrenous disposition, and most fetid smell; scabies; crusts; a dry and gentle leprosy; violent, piercing, universal, nocturnal pains; livid spots. (4) Fevers of many sorts, hot, malignant, intermitting all manner of ways, vague, periodical, continued, occasioning an atrophy; vomitings; diarrhea; dysenteries, severe stranguries; faintings; and an oppression upon the precordia, often suddenly mortal; a dropsy; consumption; convulsion; tremor; palsy; contraction of the sinews; black spots; vomiting and purging of blood; putrefaction of the liver, spleen, pancreas, and mesentery."

Boerhaave believed scurvy to be due to a peculiar condition of the blood in which one part of this fluid is too thick and viscid, while at the same time the other part is too thin, dilute, and acrid. It is not surprising, therefore, to find that this great Dutch physician had no definite ideas concerning either the prevention or treatment of scurvy. He evidently set before himself a difficult task, that of diluting one part of the blood, while at the same time he concentrated another portion of the same fluid. He wrote:

"That part of the humour which is too thick, viscid, and stagnating, must be attenuated, rendered thinner, and put in motion; meanwhile what is already too thin, is to be inspissated, and the predominating acrimony corrected, according to its different kind and species."

No wonder Boerhaave came to the conclusion that the cure of scurvy was a masterpiece of art.

In 1734 Bachstrom, a Dutch physician, published a book on scurvy which, although containing nothing new, adds some interesting bits of information. He tells of the prevalence of this disease in the garrison when Thorn was besieged by the Swedes. From five to six thousand of the soldiers in the city, together with a large number of the inhabitants, are said to have suffered from this disease. As soon as the fort surrendered and the gates of the town were opened and fresh vegetable food brought in, the mortality ceased and the disease disappeared. The same author tells how a man with scurvy, discharged from a boat on the shores of Greenland, soon recovered perfect health by feeding upon the abundant growth of sorrel and scurvy grass. Bachstrom made an interesting and valuable suggestion when he recommended that watercresses and similar plants should be grown in window-boxes and other suitable places in fortified towns which may possibly be besieged. When the Austrian Army was stricken with scurvy in Hungary in the war against the Turks the army sent a request to the medical faculty at Vienna for suggestions and help in their attempts to get rid of this disease. It is generally stated that the prescription and advice of the Vienna faculty was of no service, and this is possibly true, but Kramer, chief physician of the Austrian Army, makes the following statement concerning the reply of the Vienna faculty:

"We have received your accurate account of the scurvy, which commits such dreadful havoc among the Imperial troops in Hungary, and it is ordered to be printed directly. After weighing all circumstances the first rule we prescribe is great attention to the nonnaturals. Without this, the most heroic medicines may fail; but when a proper regard is had to this, simple remedies will do great things. As the sources of this calamity seem to be impure air and an unwholesome marshy soil, the troops must often shift their quarters and be removed into better air. * * * As the cure (after deprecating and disapproving of the use of mercury) we advise antiscorbutics of the vegetable kind to be given. *The juice, extract, tincture, decoction, etc., of these, may be administered either in whey or broth. As you have none of these plants, we have sent you their seeds to be sown in the country, and until such time as they grow up, have supplied you with a quantity of the dried herbs and of this inspissated juice.*"

This idea of growing plants to supply soldiers and sailors with fresh vegetables is an interesting and valuable one. Parry, in his first polar expedition, reported his attempt along this line as follows:

"I began also about this time to raise a small quantity of mustard and cress in my cabin, in small shallow boxes, filled with mold, and placed along the stove pipe; by this means, even in the severity of the winter, we could generally insure a crop at the end of the sixth or seventh day after sowing the seed; which, by keeping several boxes at work, would give to two or three scorbutic patients nearly an ounce of salad daily; even though the necessary economy in our coals did not allow the fire being kept in at night. The mustard and cress thus raised were necessarily

colorless from privation of light, but as far as we could judge, they possessed the same pungent aromatic taste, as if grown under ordinary circumstances, and appeared to be equally efficacious."

After scurvy had seriously developed in the English Army in Mesopotamia during the World War, gardens were planted all along the line of communication from the sea to the front and supplied large amounts of fresh vegetables to the soldiers.

In 1752 appeared the first edition of the great work on scurvy by Lind. This author was a surgeon in the British Navy and recognized that scurvy was one of the most, if not the most, destructive diseases in that line of service. The death rate from this disease was high and it not infrequently happened that whole crews were incapacitated by it. Lind made a thorough review of all preceding literature, and he made direct experiments by placing his scorbutic patients on different diets. His results were so conclusive that they could not be questioned, although nearly 50 years elapsed before the British Admiralty could be induced to add to the sailors' diet proper antiscorbutic portions. This was finally done in 1795, and the basis upon which most of the evidence in favor of it was formulated, is to be found in the work by Lind. As we have already seen, citrous fruit, especially oranges, had been known to possess the property of preventing and curing scurvy for at least two centuries before Lind wrote. There had been, however, up to his time no scientific and positive demonstration of the value of fruits, especially in the cure of scurvy. Since there were always at that time abundant cases of this disease in the English Navy, Lind divided his patients into groups, taking them in as nearly the same condition as possible. He says that they all had putrid gums, spots, and lassitude, with weakness of their knees. The basic diet of all these men who were placed together in the forehold was the same. To one group he gave elixir of vitriol; to another, two spoonfuls of vinegar; to another, sea water, a half pint every day; to another, cider; to another group, two oranges; and to still another group, one lemon each day. Those having the oranges recovered practically within six days when they were again fit for duty. Next followed the ones who had the lemons, and in the third place, the ones who had the cider, while those who had the elixir of vitriol, the vinegar, and the sea water were in no way benefited.

There is a tradition that Dutch sailors in their frequent commerce with Sicily, Portugal, and Spain learned that eating oranges would both prevent and cure scurvy. Mead says that when the English fleet was in the Baltic in 1726 the sailors were severely afflicted with scurvy. The ships had recently come from the Mediterranean and had taken on board great quantities of lemons and oranges at Leghorn. The admiral, having heard of the efficacy of these fruits in this disease, had boxes brought upon the decks each day and the fruit was distributed *ad libitum* among the sailors. Be-

sides eating what they liked, they mixed the juice with beer and pelted one another with the rinds, so that the decks were always strewn with the fruit and fragrant with the liquor. The result was that the admiral in due time brought all his sailors home in good health.

One of the most disastrous voyages made by an English fleet was, so far as scurvy is concerned, that executed under Lord Anson, which left England in 1740 and returned in June, 1744, he having lost during his voyage about two-thirds of his men. On this voyage scurvy seemed to manifest an unusual and almost incredible virulence. The chronicler tells of a sailor who fifty years before had received a wound at the Battle of the Boyne and which had soon healed. Under the disease the wound broke out afresh and appeared as if it had never healed. The callus of a broken bone which had been completely formed for many years was dissolved and the fracture seemed as if it had never healed.

“Indeed, the effects of this disease were in almost every instance wonderful. For many of our people, though confined to their hammocks, appeared to have no inconsiderable share of health; for they ate and drank heartily, were cheerful, and talked with much seeming vigor, and with a loud strong tone of voice; and yet on their being the least moved, though it was only from one part of the ship to the other, and that in their hammocks, they have immediately expired. And others who have confided in their seeming strength, and have resolved to get out of their hammocks, have died before they could well reach the deck. And it was no uncommon thing for those who could do some kind of duty, and walk the deck, to drop down dead in an instant, on any endeavors to act with their utmost vigor; many of our people have perished in this manner, during the course of this voyage.”

Upon reaching the Island of Juan Fernandez, 167 sick were put on shore, besides at least a dozen who died in the boats on being exposed to the fresh air. These sailors were so exhausted that they recovered very slowly. The chronicler says that for the first ten or twelve days they buried rarely less than six each day and of those who survived many recovered by very slow and insensible degrees.

During a part of this voyage the sailors had an abundance of fresh water on account of the heavy rains; they had plenty of fresh meat, having taken on hogs and fowls at Païta, and were able to catch a great abundance of fish each day. Notwithstanding these food-supplies, the squadron met with no noteworthy relief until it arrived at the Island of Tinian, where they obtained citrous fruits in great abundance, and it is said that within a week's time there were but few who were not so far recovered as to be able to move about without help. The commander of this fleet afterwards became Lord of the Admiralty and apparently was in sympathy with Lind and other naval surgeons in their attempts to secure an antiscorbutic ration for the British Navy and in which, as we have already stated, they succeeded in 1795.

In April, 1794, the *Suffolk*, a man-of-war of 74 guns, sailed from Eng-

land to Madras, making a voyage of 23 weeks and one day. On this voyage two-thirds of an ounce of lemon juice with two ounces of sugar were mixed with each sailor's daily allowance of grog. Scurvy began to show itself in the course of the voyage, but on an increase in the quantity of lemon juice the disease disappeared and the Suffolk reached Madras without the loss of a single man and with her crew absolutely free from scurvy.

The justly famous Captain Cook was able to make his voyage of discovery around the world (1772-1775) in the *Resolution* with a company of 118 men, covering a period of three years and eighteen days, with the loss of only one man and with no scurvy, because he looked after the health of his men. It is a matter of record that Cook provided abundantly for antiscorbutic food. He carried hogsheads of sauerkraut, of which a pound was issued twice a week to each man, sometimes oftener. Besides the sauerkraut, Cook carried with him a large supply of malt and he made a fresh brew each day, issuing from one to three pints to each man. We find no record that Cook carried citrous fruits or their juices, though it is more than likely that he occasionally supplied himself with these on his voyages.

Notwithstanding the evidence furnished by Lind and others, scurvy continued to make serious inroads from time to time in the British Navy. In the month of August, 1780, a squadron, after a cruise of ten weeks in the Bay of Biscay, returned to Portsmouth with 2,400 cases of this disease.

In 1780, 1,457 cases of scurvy were admitted to Haslar Hospital, the large British Naval Hospital; in 1810 one of the physicians at this hospital testified that he had not seen a case of scurvy in the hospital for seven years. The special antiscorbutic item in the ration of the sailor was one fluid ounce of lemon juice served with an ounce and a half of sugar daily after the ship had been at sea for a fortnight. The English Merchant Marine continued for some years to neglect, from time to time at least, to supply its sailors with proper antiscorbutics, and consequently suffered occasionally from epidemics of scurvy. Possibly the navy would not have acted at the time it did had it not been that in the spring of 1795 scurvy appeared alarmingly in the Channel Fleet. The winter had been extremely severe and vegetables were high and difficult to obtain. Fresh meat was issued to the sailors only one day a week. In April scurvy had penetrated every ship and so great was the threatening of the scourge, that Budd says:

“Fresh meat, together with a plentiful supply of oranges and lemons, was granted. Vegetables at first could be procured only in small quantities; as the season advanced, they became more plentiful, and after the thirty-first of May, 5,000 weight of salad was distributed daily among the ships at Spithead. The good effects of these refreshments were astonishing; on the twelfth of June the squadron sailed again in good health.”

Scurvy has in several instances influenced the fate of exploring parties, both in Arctic regions and in arid countries under tropical or subtropical

climate. An illustration of the latter is afforded by the history of the Burke Expedition into the interior of Australia as told by Beckler. It seems that some 20 gallons of lime juice had been prepared for this expedition, but it was regarded of so little importance that it was left behind. The expedition was undertaken during the dry season and the country was quite arid and free from all green vegetation. The men carried packages of dried vegetables, but had they been familiar with the history of scurvy they would have placed no reliance on these. Beckler says:

“Of our preserved vegetables there is little good to be said. We had only a few packages of dried assorted vegetables, the properties of which had been so preserved by the mode of preparation that we were justified in expecting them to make up in a measure for the want of fresh vegetables. By far the most of our supply consisted of unassorted vegetables of various kinds, dried and pressed, which I am bound to say, without bias, that I consider to have been useless.”

Beckler attributed the scurvy to the bad drinking water to which the men were compelled to resort, and he justified this conclusion by the statement that the rescue party, which, by the way, traversed the same region in the rainy season, had no scurvy. It is more than probable that the rescuers found throughout the country which they traversed, not only better water, but an abundance of edible vegetables. Peekey reports that scurvy is not uncommon among the shepherds in the interior of Australia when they live on salt meat and bread, but during the rainy season juicy plants spring up and, although these are disagreeable to the taste, they have antiscorbutic properties.

In 1842 Budd wrote as follows:

“The causes which in the middle of last century had rendered scurvy less frequent on land than previously have continued to operate with increasing efficiency; so that at present, except under peculiar circumstances, the disease is never met with in England, and, we believe, very rarely in any of the northern countries of Europe. That it should, a century or two ago, have been endemic in many parts of England seems almost incredible, when we consider the circumstances under which it arises, and the present aspect of this country; but we have undeniable evidence of the fact, and it affords proof of the extraordinary change which a few centuries have wrought in the cultivation of the soil, and in the habits of the people, especially with reference to the increased consumption of vegetable food. This is confirmed by the historical fact that, until the commencement of the sixteenth century, no salads, carrots, turnips, or other edible roots were grown in England. The little of these vegetables that was used before that time was imported from Holland and Flanders; and in the reign of Henry VIII, Catherine, when she wanted a salad, was obliged to dispatch a messenger thither on purpose.”

During our Civil War (1861-1865) there were 30,714 cases of scurvy recognized among the white soldiers in the Federal Army and 383 deaths attributed to this disease.

According to Wilcox, there was enormous wastage, caused by scurvy, in the Mesopotamian campaign in the World War among Indian troops,

as many as 11,445 cases occurring in the last six months of 1916. Most of these were so crippled as to be entirely unfit to undergo the hardships of active service in the field and were evacuated to India. As we have stated elsewhere, beriberi prevailed among the European troops in Mesopotamia, while scurvy raged among the Indian troops. Table I shows the rations issued to these troops.

Table I

<i>Field Ration of British Troops</i>			
Bread	1 lb.	Sugar	2½ ozs.
Fresh meat	1 lb.	Salt	½ oz.
Bacon	3 ozs.	Pepper	⅓ oz.
Potatoes	1 lb.	Fuel	3 lbs.
Tea	1 oz.		
<i>Field Ration of Indian Troops and Followers</i>			
Atta	1½ lbs.	Ginger	⅓ oz.
Fresh meat	4 ozs.	Chillies	⅓ oz.
Dhal	4 ozs.	Turmeric	⅓ oz.
Ghi	2 ozs.	Garlic	⅓ oz.
Gur	1 oz.	Salt	½ oz.
Potatoes	2 ozs.	Fuel	1½ lbs.
Tea	⅓ oz.		

It is the opinion of Wilcox that the absence of scurvy from the European soldiers was largely due to the fresh meat. He says that the ration of lime juice supplied up to the end of 1916 had no antiscorbutic value. This was replaced later by fresh lime juice prepared in India and preserved by the addition of 5 per cent alcohol and two grains to the pint of salicylic acid. This preparation had antiscorbutic properties and was of value in the treatment of patients suffering from scurvy. After the occupation of Bagdad, juices were prepared from limes and bitter oranges obtained locally and preserved as above indicated. This was issued to troops and had undoubted antiscorbutic value. Wilcox says:

“Attempts were made by the army to grow vegetables for the troops; but it was impossible to do this in sufficient quantity since in Mesopotamia irrigation is essential for cultivation and a scheme for growing vegetables for the army on a large scale would have taken a very long time to carry out. Also the art of growing fruit and vegetables successfully in Mesopotamia demanded a long and intimate experience of local conditions, and it was found that this could be more economically and satisfactorily carried out by the native Arabs under our supervision, the produce being purchased from them by the army.”

The freedom of the Indian troops from beriberi is attributed to the large amount of atta in their ration. Atta is a coarse wheat flour containing the germ and some of the aleurone layer of the grain, and consequently rich in antiberiberic substance. A preparation of condensed yeast, known as

marmite, was tried on account of its supposed antiberiberic properties and in Wilcox's opinion it proved of value in the treatment of this disease.

In 1917 the bread supplied the European soldiers was made from flour to which from 25 to 75 per cent of atta was added. Bread made from this mixture did not rise so well and was heavier than that made from wheat flour, but the change was believed to be beneficial in the eradication of beriberi. In conclusion, Wilcox says:

"The experiences of war especially in distant countries such as Mesopotamia, called for special attention to the scientific rationing of troops. The old idea of sufficiency of calories, or of proteins, fat and carbohydrates is quite inadequate to meet the needs. A dietary to be satisfactory must contain proteins, fat, and carbohydrates in the proper amount and also must satisfy the calorie requirements. In addition it is essential that it should be adequate as regards vitamin content, e.g., it must be protective against scurvy, beriberi and other deficiency diseases."

That scurvy is still of interest is shown by the fact that in 1921 it was scattered over both European and Asiatic Russia, and was especially prevalent in the Red Army. For many years scurvy has been common enough among the native mine workers in South Africa to prove of economic importance and to justify an investigation of the antiscorbutic properties of the fruits and vegetables of that country. In this study the preeminence of the orange, including the mardarins and tangerines, has been maintained. There is said to be promise in the pawpaw, but the evidence on this point is not conclusive.

Theories of Scurvy.—Quite naturally, those who saw this disease principally or altogether among sailors, came to the conclusion that it was due to an excess of salty food. Quite evidently, this did not apply, at least in all instances, to scurvy, as the disease appeared among soldiers and civilians. Kramer, chief physician of the Austrian Army which suffered so severely in Hungary early in the eighteenth century, states that his troops, especially in the spring of 1720 when the disease was most rife, ate no salt beef or pork but had plenty of fresh meat at very low price. Nitzsch, in 1747, wrote a history of scurvy in the Russian Armies, and states that at no time when this disease was especially prevalent were the soldiers confined to a salty diet. He describes this disease as it appeared in the siege of several places and in all instances the soldiers had considerable quantities of fresh meat, and especially fish. Lind pointed out that the men who worked and lived almost continuously in the great salt mines of Poland have never been known to suffer from an epidemic of scurvy. The same authority, as we have already seen, administered sea water to his patients in considerable quantities daily, and while it did them no good, it added in no way to the progress of the disease.

About the middle of the eighteenth century there was a marked epidemic of scurvy among French prisoners held in England. These men had had

no salty food. They had been fed upon fresh bread and meat, but had had no vegetables. From time to time during the nineteenth century scurvy appeared and reached epidemic proportions in prisons, almshouses, and insane asylums in England and in the United States, and in no instance could these epidemics be attributed to salty food, but in all there were deficiencies in fresh vegetables.

So far as we can ascertain, there is only one error in Lind's conclusions concerning the causes of scurvy. He carried out his experiments with food scientifically, but he never rid himself of the idea that weather, especially cold and wet, had much to do with predisposing to this disease. He wrote as follows:

"It is observed, that an intense degree of cold such as the inhabitants suffer during the hard winters in Iceland, Greenland, the northern parts of Russia, etc., together with the diet the poor are necessarily obliged to use during that rigorous season, infallibly gives rise to this disorder. And here we cannot but remark the pernicious effects of cold in augmenting its malignity, and rendering it a much more frequent and virulent distemper in these northern countries, than in warmer climates. It may, however, be doubted, whether the most intense degree of cold, provided the air is dry and pure at the same time, would breed this malady. For all these northern countries are subject to great fogs, not only in summer, but in winter; when the cold is excessive or pestered with what is called 'frost-smoak;' a vapor which rises out of the sea like smoke from a chimney, and is as thick as the thickest mist."

In studying the history of epidemics of scurvy, one is impressed with two things which stand out prominently. The first is, that in the histories of scurvy in besieged cities the disease is more likely to occur and more certain to be severe when the siege begins to operate in late winter or early spring, and the observation amounts to the same thing when applied to this disease among sailors. Ships or fleets starting on long voyages late in winter or early in spring are apparently more likely to develop scurvy early and abundantly than is the case on ships going to sea in the fall. The explanation for these two sets of observations amounts to the same thing. In a city with the people living under conditions that prevailed in northern Europe two or three hundred years ago, the inhabitants would be on the verge of scurvy with the approach of spring under natural conditions. If held in the city by a siege beginning in the spring, the continued absence of fresh vegetables from the diet would hasten the appearance and increase the virulence of the disease. Sailors who had spent the summer on shore or in ports where they had an abundant supply of fresh vegetable food, could go to sea on a long voyage in the fall much better protected against the scurvy than they would have been had they started late in winter or early in spring after months during which they had had but a limited supply of fresh food. Other than conditions like this, weather has, so far as we can see, no influence either upon the appearance or

virulence of an epidemic of this disease. As we have seen, the first recorded epidemic of scurvy occurred among the crusaders in Egypt, and we are informed by the chronicler of the Anson Expedition that the warm weather of the tropics gave to the seamen on this voyage no surcease from the virulence of the disease.

About the same time that Lind wrote, much was being said concerning the influence of the bad air on ships in the causation of scurvy; in fact, one of the earliest attempts to ventilate the hold of a ship was made with the idea that success in this direction would aid in the elimination of this disease. Lind held that neither bad air, crowding, nor filth played any important part in the causation of this disease and he unequivocally showed that improvement in these conditions had no effect upon the progress of the disease. He pointed out that the ship's carpenters were compelled to work in the foulest air of the hold and that they were not more susceptible to the disease nor did they suffer more severely than those who spent a large portion of their time on the open deck. The record is made that in the disastrous Anson voyage there was no abatement in the disease at times when it was possible to keep all the ports open to admit an abundance of fresh air. Lind also made it plain that patients with scurvy improved quite as readily and rapidly with a change in diet, whether kept on board or transferred to shore. When a ship with a scurvy crew came into port the one thing essential to cure the men was to furnish them with an abundant supply of fresh fruit and vegetables, and it made no difference whether the men remained on board the ship or were placed in hospitals on the shore.

It was thought by some that bad drinking water had much to do with the causation of scurvy. This opinion was especially expressed by those who wrote of the disease in the Russian and Austrian Armies, and it is a matter of interest that one of the first attempts to use a sand filter for the purification of river and lake water was made by Austrian physicians in the wars of their country with the Turks. We give herewith a description of one of these filters:

"A long small boat is divided into several different apartments by cross partitions. They fill them all, except the last, with sand. The boat is put into the lake. A hole level with the surface of the water is made in the end of the boat, which lets the water into the first division; from this it gets into the second by a hole made in the bottom of the first partition; from the second it runs into the third, through a hole in the top of the second partition and so alternately above and below, that it may be obliged to pass through all the sand. At the top of the last division there is a pipe, through which the water comes, at pleasure, as pure as from a fine spring."

It will be admitted that this was no mean way in which to secure a supply of safe drinking water.

From time to time, and even recently, some one has suggested that scurvy is a contagious disease. This idea was contested very forcibly and conclusively by Lind, and, in fact, it has never had any support from those best situated and most competent to study the disease. On this point Budd wrote in 1842 as follows:

“We have already seen that scurvy may occur in all climates, either on land, or at sea; in persons who subsist on salt meat or fresh; and in situations in which the utmost attention is paid to cleanliness and ventilation. There is one condition, however, which is necessary for the production of scurvy; namely, prolonged abstinence from succulent vegetables or fruits, or their preserved juices as an article of food. When this condition is fulfilled, we find scurvy arising in persons whose situations are the most various in every other respect in which we can compare them; while not a single instance can be cited of its occurring in a person well supplied with these vegetables or fruits. This circumstance, together with the fact that scurvy is, in all cases, rapidly cured when a supply of these vegetables or fruits is furnished, leads us to consider the abstinence in question as its essential and sole cause. We have said that this abstinence can be prolonged; and it would seem, indeed, that in a person previously well supplied with vegetable juices, abstinence of from two to five months is necessary to produce the disease. On land, scurvy has shown itself, always towards the end of winter or in spring; at sea, it has appeared after voyages of very different durations; in some cases, at the end of a month or six weeks; in others, after the lapse of five or six months. This difference depended upon the time of year when the vessel left port, or rather on the previous diet of the men. Attention to this circumstance will serve to explain all the apparent anomalies which have forced writers on scurvy to have recourse to such a variety of causes.”

Among recent claimants of the bacterial causation of scurvy may be mentioned Jackson and Moody. They claim the discovery of a diplococcus which causes scorbutic lesions in guinea pigs and rabbits even when these animals are fed on an antiscorbutic diet.

Antiscorbutic Foods.—If young, growing guinea pigs of about 300 grams weight be fed exclusively on oats and bran with milk heated to 120° C. for one hour, scurvy develops in these animals in from ten to twenty days and death occurs in about 30 days. This gives opportunity to test the antiscorbutic value of different foods. The food to be tested is added in variable quantity to the scurvy diet, and its success or failure to prevent the development of the disease is noted. In this way tables have been prepared showing the relative antiscorbutic value of different foods. These findings are, however, to be accepted with some caution, because the antiscorbutic value of a food depends not only upon its presence in the diet, but upon the amount added and the condition of the food at the time it is consumed. As we have seen from the earliest records of this disease, the antiscorbutic value of oranges and lemons has been recognized. In the early reports there is no mention of limes; indeed, we believe that West Indian limes were not known in Europe two hundred years ago, or even one hundred

years ago. When an antiscorbutic ration was introduced into the British Navy in 1795 *lemon* juice was chosen and continued to be the agent employed for many years. During the early part of the nineteenth century the English obtained lemons from the Mediterranean region where they were secured in unlimited quantity, in good condition, and at a reasonable price. In the third quarter of the nineteenth century the British West Indies began to produce sour limes in large quantity and lime juice was substituted in the English Navy for lemon juice as the antiscorbutic ration. It is worthy of note that the lime juice supplied the British Navy was frequently found adulterated.

In 1850 the Investigator, supplied with lemon juice, made a Polar expedition. This ship left England in January, 1850, and reached the ice regions during the following summer. Throughout the next winter and spring the men on this expedition engaged in sledging Arctic explorations and had no scurvy. In the autumn of 1851 their rations were reduced to two-thirds and the lemon juice ration was cut in two, and still there was no scurvy during the following winter and spring. In May, 1852, the first case developed—27 months after leaving England and with a large reduction in ration and lemon juice during a part of this time. More than 15 months passed before this crew was rescued and during the whole period of its absence from England, three and one-half years, there were only three deaths from scurvy.

In 1875 the Alert and the Discovery sailed from England in search of the North Pole. The antiscorbutic ration furnished this time was *lime* juice. The men on this voyage had their first taste of scurvy in January, 1876, and during the following summer and fall the disease developed abundantly and with great severity. This expedition returned to England in October, 1876.

From a study of the history of these expeditions one sees the inferiority of lime juice compared with lemon juice as an antiscorbutic. Recently, Chick, Hume and Skelton have compared by experiments on guinea pigs, as above stated, the relative values of lemon and lime juices. In order that there might be no mistake the same test was made upon monkeys. The conclusion reached is that the value of fresh lemon juice is approximately four times that of fresh lime juice. It will be remembered that in his investigations Lind gave preference to oranges over lemons, and, so far as we know, there has been no contradiction of Lind's conclusions. The three principal citrous fruits, so far as their antiscorbutic properties are concerned, should appear in the following order: oranges; lemons; limes; with oranges and lemons of nearly equal value and with limes only one-fourth as effective as the other two. Lind recommended a concentrated orange or lemon juice with alcohol in some form as a preservative. Experience, however, has demonstrated that the fresh juices are much superior to the

preserved preparations. The juices of oranges and lemons may be boiled for a short time without appreciable loss in efficiency, but when subjected to continued heat or higher temperatures under pressure their antiscorbutic properties are materially decreased. Even when these juices are kept in cold storage without the previous application of heat, after a few months there is a marked decrease in their efficiency. The addition of only three c.c. of unheated fresh orange or lemon juice to the scurvy diet as given above, protects guinea pigs from the disease, but when the juice has been kept, even in an ice-box and protected from an excess of air, after six months this quantity will not protect; indeed, double this amount fails to do so. It is important, therefore, to understand that lime juice has but little antiscorbutic value and that orange and lemon juices are most efficient when freshly prepared. If these juices are made alkaline and allowed to stand for a relatively short time, their value falls rather rapidly. The deterioration of alkalized orange and lemon juices is hastened by the application of heat. There is, however, no objection to rendering orange juice slightly alkaline if it is immediately administered. It is probably worthy of note that subcutaneous and intraperitoneal injections of orange and lemon juices do not protect guinea pigs against scurvy. It is desirable that antiscorbutic foods should be administered by mouth. The juice of the lemon or the orange in the acid state may be evaporated to dryness in vacuo without much change in value; in fact, these juices have been used in the form of powders, this condition having been reached by spraying into a vacuum.

The following quotation from Lind is of interest:

"We are upon this occasion informed by several authors, of an old custom practiced in some parts of Norway for the recovery of scorbutic people. They expose them in a neighboring desert island in the summer season, where they live chiefly on cloudberry; and it is remarked, that, by eating plentifully of these, together with the change of air, they are restored to perfect health in a very short time. In that country, the fruits gathered by the diseased themselves, are reputed of the greatest virtue. It no doubt is the case, as by this means the patient breathes the salutary country air in the open fields. Thus a free and pure country air, with such moderate exercise as at the same time conduces to the agreeable amusement of the mind, is requisite."

The cloudberry is a variety of raspberry and it has been demonstrated by Holst and Froelich, Scandinavian investigators, that the antiscorbutic value of raspberries is quite equal to that of oranges and lemons. Preserved mulberries, sugared and cooked for one-quarter of an hour, possess and hold, for a time at least, marked antiscorbutic properties.

It has been suggested that the relative infrequency of scurvy in the French fleet is due to the fact that wine is served to the seamen of this nation as a part of the daily ration, while in the English Navy grog is given. Recent experiments, however, indicate that ripe grapes at least,

are not of high antiscorbutic potency. It was found by Chick and her assistants that the juice of the grape is only one-tenth the value of that of the orange. Some are of the opinion that the value of the green or slightly ripening grape is greater than that of the fully ripe fruit. A similar suggestion has been made concerning the influence of maturity upon other fruits. Trotter observed that scorbutic patients declined ripe guavas, while they ate green ones with readiness. He, therefore, took nine scurvy patients. To one group of three he gave lemons; to a second group, green guavas, and to a third, ripe guavas. After a week the members of the first two groups were well, while those of the last were in much the same state as before the experiment. In the early part of the nineteenth century scurvy appeared, though not alarmingly, among French soldiers stationed in Alpine regions. Fodéré believed that they were benefited by being abundantly supplied with ripe grapes. Apples and cider have slight antiscorbutic properties, but are apparently inferior to the citrous fruits. Trotter states, however, that when the English fleet arrived at Spithead on the nineteenth of September, 1795, almost every man was affected with scurvy. Large quantities of vegetables were provided, but lemon juice being scarce, 50 baskets of unripe apples were procured on the Isle of Wight and recovery from the disease on their use followed speedily. It is within the range of possibility that the potency of apples varies not only with the stage of maturity, but with the variety of the fruit.

The suggestion that scurvy has been relatively less frequent on French than on English men-of-war might be questioned. The French Navy has never been so large as the English and long voyages have not been so frequently undertaken by the French. A very superficial examination of French literature shows more than 30 outbreaks of scurvy on French ships of war between 1825 and 1880. One of these is of sufficient interest to cite. In 1867 when the French were compelled to abandon Mexico, the transport, *Castiglione*, was sent from France to Vera Cruz where it was immediately occupied by soldiers and started on its return voyage. On the twentieth day out from Vera Cruz the crew was severely stricken with scurvy and the ship was obliged to put in at the Azores where large quantities of fresh potatoes, cabbages, and other vegetables were taken on board. The crew reached Toulon a fortnight later practically free from the disease.

We have seen no estimate in this particular of the value of the mango or grapefruit. The banana is said to be without antiscorbutic value.

Fresh, green, leafy vegetables have long had the reputation of being possessed of great antiscorbutic potency. In this class, cabbage holds the lead, probably because of its wide distribution, the large amounts in which it can be consumed, the varieties in which it appears, and the ease with which it may be preserved during the winter or packed and carried on long voyages. One gram of fresh cabbage added to the scurvy diet pro-

teets guinea pigs from this disease, while one-half this amount fails to do so. Two grams relieves beginning scurvy, or when added to the diet before the disease develops apparently satisfies all nutritional needs. In antiscorbutic potency, cabbage is followed by lettuce, collards, endives, dandelion leaves, sorrel, and turnip tops. Among green vegetables the cabbage holds about the same place as that given to the orange or the lemon among fruits. Cooking lessens the antiscorbutic value of all green vegetables, though it makes a difference how long the heating is continued. Prolonged heat is more detrimental than a higher temperature maintained for a shorter time. It follows from this that the slow cooking of green vegetables is, at least so far as their antiscorbutic potency is concerned, to be avoided. Vegetable juices are more sensitive to heat than the vegetables themselves, though in this respect there are great differences in the juices.

For certain purposes it is highly desirable that some method of desiccating fresh vegetables without destroying their antiscorbutic properties should be devised. This would furnish the soldier with a valuable addition to his daily ration and would enable him to carry his antiscorbutic in his knapsack. Although repeated claims have been made and are still being made from time to time, we are not aware of the existence of any method of dehydrating without at the same time lessening food values. Cabbage is best preserved in the form of sauerkraut, but this is bulky and does not fill the want. We have already seen that dried vegetables, sent to the Austrian soldiers in Hungary during the wars with the Turks, were without value. From time to time, some enterprising genius offers to sell to the Government a formula for carrying and serving green vegetables in tablet form. Many of these rations have been tried in our own armies, as well as in those of other countries, and up to the present time they have not been a success.

Some form of green vegetable at some time of the year grows in most countries in sufficient abundance to protect the ordinary population from scurvy, but there are many places in which supplies are not at the time available for moving armies. According to Parry, the Eskimos eat sorrel which begins to vegetate in those regions about the middle of June, but we fail to find any evidence that they lay in a supply of this delectable food for the winter season.

Vegetables may be pickled and in this form retain marked antiscorbutic potency. Mertans (1770), in reporting to the Royal Society of England concerning his observations during many years of residence in Moscow, stated that he frequently saw scurvy among the well-to-do but very seldom among the working people. The immunity of the latter he believed to be due to their eating abundantly all the year around of pickled vegetables, especially cabbage. Other travelers in Russia, who have left the beaten paths or mingled with the common people, are acquainted with the great

variety of ways in which cabbages are served in that country. Among the German people sauerkraut is regarded as a most delectable dish and in its place other vegetables, especially turnips, prepared in like manner, are often preserved and eaten.

We have already given Cartier's description of how he and his soldiers were saved in Canada by drinking decoctions of spruce tops. There are many similar statements. When the Swedes invaded Russia several centuries ago, it is said that the progress of the army was arrested by a severe outbreak of scurvy and that a prompt and efficient remedy was found in the needles of the common fir, the scientific name of which was changed from *abies rubra* to *pinus antiscorbutica*. In like manner it is reported that in 1736 two squadrons of the Russian Navy were obliged to winter on the northern coast of Siberia near the mouth of the River Lena. While in their winter quarters scurvy distressed them and they found relief by cooking and eating the needles of the mountain pine, *pinus sylvestris*.

Of the tuberous foods, the potato is the most widely cultivated and most abundantly eaten. The potato, however, compared weight for weight with such fruits as the orange and lemon has but feeble antiscorbutic potency. This, however, does not mean that the potato could be easily dispensed with in protecting ourselves against this disease. Potatoes are eaten by almost everybody and are consumed in large quantities. It has been found that on a scurvy diet, 17 grams of potatoes, steamed at 100° C. for 30 minutes, do not fully protect guinea pigs against the disease. In estimating the value of the potato as an antiscorbutic Hess makes the following statement:

"It is common knowledge that outbreaks of scurvy follow closely upon a failure of the potato crop. This has been particularly the case in Ireland, where it was especially evident in relation to the great epidemic of scurvy in 1847. Holst and Froelich inform us that 'all scurvy epidemics in Norway in the nineteenth and beginning of this century followed failure of the potato crop.' Nor is this danger past. In an article entitled, 'The Rôle of Antiscorbutics in our Dietary,' the author recently reported that a partial failure of the potato crop in the eastern part of the United States led to the development of scurvy in numerous institutions, in one of which over 200 cases of definite scurvy developed in the spring of 1916."

It appears that freezing does not lessen the antiscorbutic properties of the potato. In 1857 there was a small garrison at Fort Randall, Dakota. Supplies were sent from St. Louis by boat, but on account of the ice the boat was compelled to stop 100 miles below the fort. Through this distance the supplies were carried in wagons and did not reach the men until the first week in January. The potatoes were frozen through and through, but the men ate them, both cooked and raw, with the result that the scurvy temporarily disappeared, with some show of return some weeks after the supply of potatoes had been exhausted.

Chick and her assistants have given great prominence to a tuber grown largely in England but practically unknown in this country. The common

name is *swede* and it belongs to the order Cruciferae. Of this food the English investigators say:

"The juice of the fresh raw swede easily takes the first place in respect of anti-scorbutic value. Protection from scurvy was attained with a daily ration of 2.5 c.c. In case of raw carrot juice, severe scurvy developed in animals receiving daily rations of 5 and 10 c.c.; with a daily ration of 20 c.c., protection from scurvy was secured and the general condition of the animals was about the same as of those receiving a daily ration of 2.5 c.c. of swede juice. In case of beet-root, the anti-scorbutic value was less than that of carrot; animals receiving a daily ration of 20 c.c. fresh raw juice showed only a small degree of protection, acute symptoms of scurvy supervened in every case, and death from scurvy occurred in several instances before the period of experiment, three months, had expired. It is thus seen that raw swede juice provides a valuable and inexpensive source of anti-scorbutic material. Its value is not markedly inferior to that of fresh orange juice, and it may be regarded as a satisfactory substitute; its value is ten times that of raw carrot and more than ten times that of raw beet-root juice. It has recently been adopted in some infant welfare centers, and there does not appear to be any drawback to its use for the purpose of infant feeding."

Onions, garlic, and similar foods were at one time believed to be of value in the prevention of scurvy, but their use for this purpose has apparently been discontinued.

Hess stresses the value of the tomato, even when canned, as an anti-scorbutic. He says:

"It was found, in an experiment embracing many series of guinea pigs, that 4 c.c. daily of strained, canned tomato are sufficient to afford protection, even when a lot was used which had been prepared a year previously. This is indeed remarkable, considering that the food undergoes a two-fold heating in the course of canning, during one of which (processing) the temperature is raised to fully 230° F. Tomatoes have another advantage over most other vegetables in that they are richly endowed with the water-soluble vitamin, as shown by our tests on pigeons suffering from polyneuritis, and by the experiments on rats by Osborne and Mendel, who found tomatoes far superior in this respect to turnips, onions, beet-roots or beans. They are also rich in the fat-soluble vitamin. In view of the availability of canned tomatoes and their excellent keeping quality they are well suited to an extended use as an antiscorbutic."

The cereals, leguminous seeds, or pulses, as wheat, rye, rice, maize, millet, peas, beans, and lentils are without antiscorbutic properties except when germinated. Chick found that the addition of from 30 to 40 grams daily of dried, green peas to the scurvy diet did not prevent the development of the disease in guinea pigs, while the addition of 10 grams of germinated peas did protect. The peas were kept moist, with free access of air, for 48 hours at room temperature, when they developed sprouts about 1 cm. long. In this condition they were found to have an antiscorbutic value equal to that of many fresh vegetables, but not so great as that of cabbage. Cooking reduced their value about 75 per cent.

There has been diversity of statement concerning the antiscorbutic

properties of fermented alcoholic beverages. As has been stated, Cook, on his great voyage of discovery, prepared an infusion of malt each day and made liberal distribution of this preparation to his seamen with apparently good results. The sweetwort used by Cook, however, was a preparation of germinating grain rather than one which had undergone to any marked extent alcoholic fermentation. Harden and Zilva by means of experiments upon guinea pigs and monkeys have shown that beer, as commercially prepared and bought upon the market, is without either antineuritic or antiscorbutic potency. Beverages which have undergone acetous fermentation have no value as antiscorbutics. It is true that vinegar was at one time recommended and occasionally even in recent books one finds an approval of it, but this has not been justified either by practical experience or scientific demonstration. It has been stated by Dyke that scurvy appeared during the World War in a Kaffir labor battalion in France. In their homes these people were given to the daily consumption of large quantities of a beer made from freshly germinated grain and had been free from this disease. The French, with the intention of checking the disease, prepared a beverage for the people but neglected to germinate the grain. The result was that the scurvy was neither prevented nor abated. Budd states:

“Spruce beer seems to be the most efficacious of fermented liquors. We have abundant proof in the experience of the North American colonies, and of the countries bordering on the Baltic, that it is not only an effectual preventive, but an excellent remedy. It has this advantage, that materials for it can often be procured, at all seasons, in countries in high latitudes, where the scarcity of fruits and vegetables renders a powerful antiscorbutic extremely valuable.”

At one time (about 1780) crude molasses had a reputation in the British Navy as an antiscorbutic. It is possible that the molasses of that time contained fermenting substances which are not likely to be present in appreciable amount in this food as now made. It has long been acknowledged that the antiscorbutic properties of sugar cane are greater than those of molasses and that they are much impaired by the processes used in the manufacture of sugar. Distilled liquors have been uniformly condemned from the earliest to the latest writers upon this subject. In 1781 Blane presented a memorial to the Board of Admiralty, recommending the substitution of wine for rum in the daily ration of seamen. Lind spoke in no uncertain terms in his condemnation of distilled liquors.

There can be no doubt that fresh, raw milk, human or bovine, has antiscorbutic properties sufficient to protect the infant from scurvy during the first months of its life. Both experience and scientific experiment have, however, shown that the antiscorbutic properties of milk are not great and that they are materially impaired on standing, and especially by heating. During the last 20 years of the nineteenth century sterilized milk was used almost universally in this country in the artificial feeding of infants. The

result was that nearly every physician who had many infants under his charge saw cases of scurvy. This led to the substitution of pasteurization for sterilization. Within recent years much attention has been given to the effects of both of these processes upon the antiscorbutic properties of milk. It was shown by Froelich and Funk, independently, that guinea pigs are protected from the development of scurvy if 50 c.c. or more of fresh, unheated milk are added each day to the scurvy diet. Chick and her assistants showed that if the amount of milk is less than 50 c.c. the animals develop the disease quite as promptly as do those who have had no milk. When the amount added is from 50 to 100 c.c. there is less scurvy, and with amounts of from 100 to 150 c.c. there is no scurvy. The conclusion from this is that the antiscorbutic potency of milk is not great and that adults can hardly take enough milk in their daily food to prevent the development of this disease. Hess, who has had large experience in the treatment of infantile scurvy, writes as follows:

“There is no question but that breast-milk and raw cow’s milk furnish sufficient antiscorbutic vitamin, but there is a difference of opinion as to whether pasteurized milk, or milk that has been brought just to the boiling point, or even sterilized milk, is adequate in this respect. Much of this divergence of opinion is due to the fact that the various clinicians have not considered or stated the quantity of milk which they have found sufficient to protect, and also because milk itself differs in its antiscorbutic value according to its freshness and probably also according to the fodder of the cows. Without entering once more into a discussion of this question, it may be stated that unless the cow’s milk is raw, the infant should receive additional antiscorbutic foodstuff. Moreover, this supplement to the dietary should be made as soon as possible, so as not to allow the vitamin deficiency and inadequate diet to exist for even a short period. In our experience there is no contraindication to the giving of orange juice or of strained canned tomato, the two antiscorbutics with which we have had a large experience, to babies one month of age or even younger. The common practice, however, is to wait until the infant is five or six months of age, which certainly must allow a rudimentary scorbutic condition to develop. At the age of a month one teaspoonful of orange juice may be given; it should be diluted with water and sugar added if it is tart. This may be administered notwithstanding the fact that a baby has a tendency to looseness of the bowels, as orange juice, as recently pointed out by Gerstenberger, has practically no laxative action. Occasionally babies regurgitate orange juice, but the reaction usually ceases after a day or two. If it does not, a small amount of alkali—for example, limewater or sodium bicarbonate—may be added just previous to feeding; in this state the juice will be better tolerated. The amount of orange juice should be increased so that when the baby is three months of age it receives one tablespoonful.”

It has not been fully determined whether milk dried by the new process of spraying into a vacuum retains its antiscorbutic potency or not. Hess is inclined to think it does, and says:

“The fact that milk, in spite of drying, retains this labile vitamin for so long a period, demonstrates that it is available in the most remote parts of the world, and that the possibilities of its transportation are unlimited.”

There is still opportunity for diverse opinion concerning the antiscorbutic potency of fresh meat. Writing in 1842 Budd stated:

"The opinion that scurvy can be prevented, or cured by fresh meat, is, however, still held by persons, by whom it is of the utmost importance that correct notions on this subject should be entertained. We have known the most fatal effects result from the erroneous opinions of captains of merchant vessels on this point. During the course of the present year, the captain of a vessel trading to the Mauritius furnished his men while they stayed at the Island, with a plentiful supply of fresh beef, which, being imported from Madagascar, is procured at considerable expense; but neglected to provide them with vegetables or limes, which abound in the Island, and are sold at a price scarcely worth naming. The consequence was that scurvy broke out soon after they set sail; and before the ship arrived in this country, one-half the men before the mast had died of it, and the rest were totally disabled."

On the other hand, Stefánsson and his men lived free from scurvy in the Arctic regions and fed exclusively upon the meat of seals and Polar bears. It will be easily understood that many kinds of meat go under the designation of *fresh*. Meat imported from Madagascar into Mauritius was probably called fresh because it was not salted or dried. Its freshness, however, must differ in degree materially from that of the animals which Stefánsson and his companions killed on the ice fields and immediately consumed. There seems to be no doubt that man can live and retain his health upon an exclusively meat diet, provided he gets it immediately after the death of the animal and consumes it in large quantity.

So far as experience and experiments have gone, what is said of the antiscorbutic value of meat applies to that of eggs. Hard boiled eggs are practically without antiscorbutic value, and even raw eggs added to the dietary are not sufficient to cure scurvy.

Infantile Scurvy.—It has long been recognized that scurvy may occur at any age. As long ago as 1778, Mertans, reporting on this disease as he observed it in the Foundling Hospital at Moscow, stated that it appeared there every spring among the children and that in one year he had seen as many as 60 afflicted with this disease.

In 1883 Barlow collected a number of cases, some from his own practice, others from reports made by his colleagues, and still others from the literature, generally reported as acute rickets. From a study of these, Barlow concluded that the basic disease in these cases was scurvy, which appeared sometimes in conjunction with rickets and at other times quite independently of this disease. Barlow's contention that these cases were actually scurvy was based upon the demonstration of the presence of subperiosteal hemorrhage, especially at the lower end of the femur, with or without sponginess of the gums, and upon the fact that these cases promptly recovered on an antiscorbutic diet. It is proper to note here that Barlow gives credit to Cheadle for the earlier recognition of similar cases of scurvy. He says:

"Cheadle insisted that the obscure symptoms referable to the bones and the cachexia were not explicable by either rickets or congenital syphilis. But in 1878 three cases were fully described by Cheadle in which definite sponginess of the gums occurred and likewise obscure symptoms referred to the lower limbs. These cases he claimed on clinical grounds to be true scurvy. In 1879 and in 1882 Cheadle published further examples and he suggested that the disease could be grafted on rickety stock. Cheadle's papers laid down the original lines of the true interpretation of the disease which we have to consider, and I do not think that anything has invalidated the soundness of his conclusions."

Notwithstanding Barlow's full recognition of Cheadle's priority in the correct interpretation of these cases, infantile scurvy has come to be known, especially in Germany, as Barlow's disease. In 1894 Barlow wrote more fully concerning infantile scurvy, and in this contribution he states that the condition of the gums depends largely upon whether or not teeth have appeared. He says:

"If several teeth have appeared, considerable sponginess of the gums may be manifest. Fleishy swellings form, which even project from the mouth and give rise to bleeding and fetor. But if only a few teeth have appeared the sponginess may be slight though definite, forming a narrow, fleshy ridge round each tooth. If no teeth have appeared the gums may be normal or may present small, bluish extravasations over the sites of the oncoming teeth."

In his second communication Barlow held that at that time (1894) infantile scurvy was increasing in England and was more frequently seen among the rich than among the poor. This he attributed (1) to the increasing difficulty to get fashionable mothers to suckle their infants; (2) to the frequent use of proprietary foods among the rich; (3) to the fact that the poor give their children a mixed diet at a much earlier period than do the rich. While Barlow recognized the frequency with which infantile scurvy was due at that time to the employment of proprietary foods, he also expressed the opinion that many cases were due to condensed and to heated milk.

In 1892 Northrup reported 11 cases of scurvy in infants and in 1898 a committee of the American Pediatric Society made a collective investigation and report upon this disease in this country. The members of this Committee were of divided opinion. The majority reached the following conclusions:

"(1) That the development of the disease follows in each case the prolonged employment of some diet unsuitable to the individual child, and that often a change of diet which at first thought would seem to be unsuitable may be followed by prompt recovery. (2) That in spite of this fact regarding individual cases, the combined report of collected cases makes it probable that in these there were certain forms of diet which were particularly prone to be followed by the development of scurvy. First in point of numbers here are to be mentioned the various proprietary foods. (3) In fine, that in general the cases reported seem to indicate that the farther a food is removed in character from the natural food of a child the more likely its use is to be followed by the development of scurvy."

The minority report concluded as follows:

“(1) From a study of this report and from due consideration of other known facts, scurvy appears to be a chronic ptomain poisoning due to the absorption of toxins. (2) It follows the prolonged use of improper food and abnormal intestinal fermentation is a predisposing factor. (3) Sterilizing, pasteurizing, or cooking of milk food is not *per se* responsible for the scurvy condition. (4) A change of food and the administration of fruit juice and treatment of any underlying cause is the rational therapeutic procedure in scurvy.”

It is generally stated by pediatricians that infantile scurvy is most common during the second six months of life. Barlow states that the physician should be especially on the lookout for this disease about the eighth month and that it occurs most frequently between this and the eighteenth month. Crandall finds in the literature one case in which the disease was recognized during the fourth week of life; another, one and one-half months old; three, two months, and seven under four months. There are cases reported in which the child has taken its food exclusively from the breast, but in most of these the mother's health was not good, while in some the statement that the child was exclusively breast-fed is questioned. A wet nurse was nursing her own child with another when the foster child became scorbutic while her own remained healthy. Crandall says the inference to be drawn in this case is clear.

Experimental Scurvy.—In 1895 Smith (Theobald) reported that when guinea pigs are fed on bran and oats without grass or other succulent vegetable substances, they manifest subcutaneous extravasations of blood and die within from four to eight weeks. In 1903 Bolle found that guinea pigs fed exclusively on milk, raw or sterilized, die after a short time and show at autopsy unusual fragility of the bones. He accordingly claimed that these animals died of scurvy, but his demonstration was not altogether convincing. In 1905 Bartenstein repeated these experiments and showed that the bones become fragile, are easily broken and subject to spontaneous fracture. This demonstration was also regarded as insufficient to justify the claim that these animals had scurvy. The first convincing experimental work along this line was carried out by Holst and Froelich in 1907, from which time the experimental development of this disease in these animals has been admitted and, as we have already seen, a standard scurvy diet has been employed in determining the relative values of anti-scorbutic foods. The symptoms and lesions of this disease in the guinea pig are quite similar to those in man, although hemorrhage in the gum is not common. Subperiosteal hemorrhages do occur and separation of the epiphyses may result. The cecum is often distended with accumulated food, but this varies with changes in diet. It is, however, so marked that some are inclined to ascribe the development of the disease in these animals wholly to arrest of the food in this portion of the intestine and the absorp-

tion of bacteria or bacterial products through the thin walls of the alimentary canal.

Hess and Unger say:

"All diets leading to scurvy in the guinea pig produce scurvy in man; all antiscorbutics are potent for both species; all signs and symptoms of the disease are common in some degree to both guinea pig and man. There is, however, one important difference, namely, that in man the disorder is a slow, markedly subacute process, whereas in the guinea pig it is almost an acute disease. This does not mean that this animal is not suitable for the study of scurvy, but merely that it is a hypersensitive reagent, and therefore not well adapted for even quantitative experiments."

The monkey is the only other experimental animal in which lesions closely similar to those in man occur when this animal is confined to a scurvy diet. The animal becomes apathetic and one of the first signs is hemorrhage in the gums. Subperiosteal hemorrhages, forming large effusions, develop in various parts of the body, especially cranial bones, scapula, and maxilla. Hemorrhage behind the eye, leading to exophthalmos, very infrequently seen in man, may develop in the monkey. Both in the monkey and in the guinea pig the beaded condition of the ribs, frequently seen in infantile scurvy, is common.

McCollum holds that the susceptibility of the guinea pig is to be found in the peculiar conformation of its digestive tract, and if we read him correctly, he thinks that intestinal stasis and renal elimination are concerned with the production of this disease in man. In 1918 he wrote as follows:

"Scurvy in the long sailing voyages of the past was probably the result, first, of the poor quality of the food (biscuits and stale meat), which did not form an adequate diet and caused depletion of the vitality of the sailors. Constipation and perhaps also, as Hess suggested from his observations on infants, failure to urinate sufficiently formed the preliminary conditions which permitted the development of the bacterial flora which finally brought on an attack of the disease. Fresh vegetable and fruit juices relieved the condition for three reasons: first, they did much to render the diet complete from the physiologic standpoint, which alone would greatly promote recovery; second, they were good correctives for the faulty elimination, because of their bulk and water-holding capacity of their indigestible residues; and third, especially in the fruit juices, the diuretic property would cause a thorough washing out of the tissues. A diet of wheat biscuits and meat is inadequate with respect to two chemical factors; its organic content is entirely inadequate, and it is lacking in the factor, fat-soluble A. What there is of indigestible residue consists mainly of protein residues, which would favor the development of a pernicious flora in the intestine. Such a tentative explanation as that just offered harmonizes well with the experimental facts. The most convincing evidence of the general correctness of this view of etiology of scurvy lies in its experimental production with diets which are known to be complete chemically, and which nourish well certain species of mammals that do not suffer from special anatomic disabilities, because of the peculiar form of the digestive tract. The relief of the disease by several means, none of which can possibly be interpreted as supplying a hypothetical curative substance, an 'antiscorbutic substance,' which

would be considered as analogous to those which are concerned with the relief of beriberi and xerophthalmia, eliminates this from the list of so-called 'deficiency' diseases."

Cohen and Mendel, as a result of experiments upon guinea pigs, combat the theory of McCollum and find that constipation, while it may aggravate the symptoms, is not an essential condition for the development of scurvy. They point to the work of Hess, who showed that the daily addition of mineral oil as a laxative to a scurvy producing diet, is not sufficient to protect or cure, while the production of marked constipation by the administration of morphin does not induce scurvy. Moreover, Hess has cured scurvy by the intravenous injections of orange juice. This they claim could not relieve constipation or in any way affect intestinal complications.

McCarrison has found that in guinea pigs kept on a scorbutic diet there is an increase in size and weight of the adrenal glands, a marked diminution in the adrenalin content of these organs, a hemorrhagic infiltration of these glands, usually circumscribed and located about the periphery of the cortex, and finally degenerative changes in the cells of the cortex and medulla. The same investigator, studying the intestinal canal of guinea pigs and pigeons kept on a scorbutic diet, finds that in these animals there result congestive and atrophic changes in the coats of the bowel, lesions of the neuromuscular mechanism, impairment of digestive and assimilative functions and failure of protective action against infection. He thinks that similar gastrointestinal changes may occur in man, but of these, so far as we know, there has been no positive demonstration.

Bibliography

- American Pediatric Society; *Archiv. Pediat.*, 1898, xv, 481.
 BARLOW, T.: *Chir. Trans.*, 1883, lxxvi, 159; *Lancet*, 1894, ii, 1075.
 BLANE, GILBERT: *Observations on Diseases Incident to Seamen*, London, 1789, J. Murray.
 BUDD, G.: *Tweedie's System of the Practice of Medicine*, Philadelphia, 1841, Lea and Blanchard.
 CHICK, H., AND DELF, E. M.: *Biochem. Jour.*, 1919, xiii, 199.
 CHICK, H., AND HUME, M.: *Trans. Soc. Trop. Med. and Hygiene*, 1917, x, 141.
 CHICK, H., AND RHODES, M.: *Lancet*, 1918, ii, 774.
 CHICK, H., AND SKELTON, R. F.: *Lancet*, 1918, i, 1; *ibid.*, 1918, ii, 735.
 COHEN, B., AND MENDEL, L. B.: *Jour. Biol. Chem.*, 1918, xxxv, 427.
 COMRIE, R.: *Edinburgh Med. Jour.*, April, 1920.
 DUTCHER, R. A.: *Proc. Natl. Acad. Sc.*, 1920, vi, 10.
 DYKE, H. W.: *Lancet*, 1918, ii, 513.
 FUNK, C.: *Die Vitamine*, Wiesbaden, 1914, J. F. Bergmann.
 HAWKINS, R.: *Purchas' Pilgrim*, iv.
 HESS, A. F.: *Scurvy Past and Present*, Philadelphia, 1920, J. B. Lippincott.
 HOLST, H., AND FROELICH, T.: *Jour. Hygiene*, 1907, vii, 634.
 HOPKINS, F. G.: *Proc. Royal Soc. Med.*, 1920, xiii, 1.
 JACKSON, L., AND MOODY, A. M.: *Jour. Infect. Dis.*, 1916, xviii, 478 and 511.
 LIND, J.: *A Treatise on Scurvy*, ed. 2, London, 1757, A. Millar.
 MCCARRISON, R.: *Indian Jour. Med. Res.*, 1919, vi, 275; *ibid.*, 1919, vii, 188.
 MCCOLLUM, E. V.: *Oxford Med.*, 1918, i, 43.
 OSBORNE, T. B., AND MENDEL, L. B.: *Jour. Biol. Chem.*, 1919, xxxix, 2.
 SHEPPARD, A. L.: *Indian Jour. Med. Res.*, 1916, iv, 340.
 STEFÁNSSON, V.: *Jour. Am. Med. Assn.*, 1918, lxxi, 1715.

CHAPTER IV

BERIBERI

ENDEMIC POLYNEURITIS. EPIDEMIC DROPSY

Description.—There have been many diverse statements concerning the etymology of the word beriberi. Bontius, an early student of this disease in Java, says that the word is derived from “bharyee,” meaning sheep, and implies that the individual suffering from this disease walks like a sheep. Marshall thinks the word of Sinhalese origin and means “feeble gait.” Herklots thinks it originates from the Hindustani word “bharbari,” meaning swelling and referring to the edematous condition of the feet and ankles. Castellani and Chalmers give a more interesting derivation from the Sinhalese term meaning “cannot” and implying that the person is too ill to work. In Japan the disease was long known under the name “kak-ke,” a word of Chinese origin and said to mean “disease in the legs.”

It is now generally believed that the essential involvement in this disease lies in the peripheral nerves, causing disorders of movement and sensation, and in some instances leading to edematous accumulations, most frequently observed in the lower extremities, though they may occur in other parts of the body. It is said to be either acute or chronic, although in reality what is known as acute beriberi is, for the most part at least, an exacerbation of the chronic form. This is the opinion of most of those who have had the greatest opportunity to study the disease, though there are some who believe that beriberi may be acute from the first, manifesting itself in violent vomiting, accompanied by marked cyanosis and dyspnea, and causing death in a few days from failure of respiration. It is customary to speak of a paralytic, a dropsical, and a mixed form, according to the absence, early or late appearance, of dropsy. The disease usually develops by slow stages, indicated by lassitude, indifference to surroundings, and inability to work. With the development of the paralytic form, there is a slow, increasing difficulty in walking, with the gradual development of marked paralysis. Less frequently, this paralysis involves the upper extremities as well, and in extreme instances the patient may be reduced to a perfectly helpless condition, being unable to walk or even to feed himself. These motor disorders are in many cases accompanied by perversions in sensation, manifesting themselves in burnings of the feet, tenderness on pressure,

and creeping sensations, especially in the limbs. As the disease progresses, the sensory disorders take the form of anesthesia, with more or less complete loss of sensation on the application of heat, cold, or pressure. The anesthetic manifestations are most common in the lower extremities, though they may extend to the upper. The evolution of these nervous disorders is accompanied by a constantly developing anemia, with palpitation and dyspnea. Anemic murmurs are heard on auscultation, and percussion reveals increasing areas of dullness due to dilatation of the heart or the accumulation of fluid in the pericardium. The pulse becomes small, compressible, and variable in time.

In other cases, edema is one of the earliest manifestations, usually beginning in the ankles and gradually extending upwards and finally leading to accumulations in all the serous cavities.

After death from the chronic form, the body may be found either shrunk, much emaciated, with the skin dry, or swollen and dropsical with edematous accumulations under the skin, especially over the lower extremities, possibly over the upper as well, and, more rarely still, over the trunk. The right side of the heart is almost invariably hypertrophied and the myocardium shows fatty degenerations, sometimes to so marked an extent that the muscle striation has disappeared. Wright found that the nervous system of the heart often shows widespread degenerative changes, although in chronic cases the degenerative alterations may be confined to the vagi. The degenerative processes in the peripheral nerves vary widely; in fact, both the axon and medullary sheath may have disappeared and the nerve fibers are lost in the connective tissue of the endoneurium; indeed, it may be found that the nerve is represented almost wholly by connective tissue. These alterations in the peripheral nerves are due to processes which have been long operative and, naturally, the degree of degeneration is determined by the intensity of the process and the time of its continuance. In less chronic cases, the peripheral nerves may appear quite normal, but upon microscopic examination they will be found to be hemorrhagic, with the most marked changes in the muscular branches in the limbs.

In more acute cases, it is not infrequent to find congestion in certain portions of the mucous membrane of the alimentary canal, especially in the esophagus, stomach, and duodenum, where hemorrhagic extravasations may appear. In these cases, the lymphatic glands in the region of the stomach and duodenum are frequently congested and enlarged. A like condition is found in the liver, which more rarely shows a nutmeg-like condition, with hemorrhagic patches scattered throughout the organ. Fatty degeneration of the liver cells, with occasional evidences of necrosis, may be found.

Braddon condenses Manson's definition of beriberi as follows:

"A form of peripheral neuritis, which occurs endemically and epidemically, and is especially characterized by proneness to edema and to implication of the neuromuscular system of the central organ of circulation; by complete absence of trophic skin lesions, of paresis of the muscles of the head and neck, of marked implication of the organs of sight, hearing, taste, and smell, and of the mental faculties; there are troubles of locomotion, paresthesias of various descriptions, especially in the lower extremities; marked hyperesthesia of the muscles involved, and subsequent atrophy."

Pekelharing and Winkler describe the initial phase of this disease as follows:

"Slight edema along the crest of the tibia; a puffy, pasty, face; difficulty in certain movements, observable only at first when the patient walks quickly or endeavors to go upstairs; some paresthesia or anesthesia of the lower extremities; palpitation of the heart, a slightly quickened pulse, or, rather a pulse which remains within normal limits while the patient is at rest, but which upon the least exertion goes up to 90 or 100 beats per minute; a marked contrast between the violent beats of the heart and the small and feeble pulse; a prolonged first and reduplicated second sound of the heart. These form a complete summary of knowledge of the symptoms of beriberi in the early stage."

History.—It has been suggested that the first notice of beriberi is to be found in the description of a disease which appeared among Roman soldiers in Arabia in 24 B.C., given by Strabo and Dio Cassius. We think it highly improbable that this disease was identical with, or had any relation to, beriberi, which, so far as we can ascertain, was never known in Arabia or among Roman soldiers in any part of the world. It is true that within very recent years a few cases have been reported under this name at Aden, but there is no record that beriberi or anything like it has ever been known in the interior of Arabia. According to Scheube, Chinese scholars find the word "kak-ke" in their writings as far back as 200 B.C., and from that time on descriptions of this disease have appeared in Chinese literature. The earliest record of the disease in the annals of Japan was made in the ninth century.

Ni, a present day Chinese writer on beriberi, at our request has furnished us with the following statement: "Che-Zee" is the term given to a disease resembling the wet form of beriberi in an old Chinese medical book, "Soo-Van," said to have been written about 2500 B.C. Since the Don Dynasty the term "Char-Chee" has been used in Chinese literature. The word "char" means foot, while "chee" means gas or something which is highly labile. In older Chinese literature it is said that there are two varieties of chee, "inn" (negative or cathodic) and "yarnn" (positive or anodic). It was believed that in the healthy body there is a properly balanced antagonistic and cooperative function between inn

and yarnn. It was believed that beriberi is due to an unbalanced antagonism of chee in the circulation, starting up symptoms in the char (foot).

The Western World knew nothing of this disease until the Dutch began their commerce with the East Indies. Bontius (1759) was the first European physician to study and describe this disease. A few years later Tulpius made a report of his observations upon a patient with this disease who had acquired it in the East Indies but had returned to Holland. There are reports made by Paxmann, Lind, and Fontana, but we have not been able to obtain copies. The oldest extensive treatise on beriberi which we have studied is a prize essay on the history and treatment of this disease written by Malcolmson, of the East Indian Medical Service, published in 1835. This author observed beriberi, especially among native regiments, both Hindoos and Mussulmen. He found more cases among the latter, but for this difference he was apparently unable to suggest any satisfactory explanation. It was observed at that time that the disease was more prevalent along the coast than in the interior, and quite naturally it was suggested that the eating of fish had some causal relation to it. Malcolmson wrote:

“Much has also been said of the effects of various kinds of food, and Dr. Herklots enumerates a number of articles whose use he considers injurious; but when we reflect that these are standard aliments all over India, we cannot carry our deference to his experience so far, as to admit, that they can produce in these districts only, so singular a train of symptoms. What effect the extensive use of fish may have, in combination with other influences, I am not prepared to say, but the comparative cheapness of all kinds of grain in the Circars, and the easy circumstances of many of the native soldiers who suffered, are fatal to any supposition of the disease depending on deficient and unhealthy diet.”

Before the publication of Malcolmson's book, Marshall and Wright, independently, had published articles upon this disease in the *Edinburgh Medical and Surgical Journal*. The contribution of the former is short but explicit and shows that he actually knew beriberi and was not confounding it with some other disease, as the earlier writers were prone to do. He wrote:

“The leading symptoms of this disease are numbness, *edema*, sometimes loss of power of the lower extremities, general *anasarca*, *dyspnea*, great uneasiness at the *precordia*, spasms, feeble pulse, livid countenance, and coldness of the extremities.”

He stated that beriberi was exceedingly prevalent among the various classes of troops employed in Ceylon about the end of the eighteenth century, but since that time it had become comparatively rare in that country. He found that Lascars or Indian seamen occasionally developed the disease, that it was found on the Malabar Coast and on that part of the Coromandel Coast which extends from Madras to Ganjam,

but that it was seldom observed more than 40 miles inland. He was of the opinion that the disease was not found in any other part of the world.

Wright (1834) discussed the disease more fully, but added nothing of special value. As to the cause, he stated that the Hindoo practitioners believed it to be due to some morbid substance with which the water and air become impregnated at certain seasons. There is no evidence, although suspected by some, that food had any causal relation to the disease.

From the first half of the eighteenth century, when this disease first came under the observation of European physicians, down to the present time, the area of its prevalence has apparently greatly extended, although it is difficult to decide in studying the disease in certain countries whether it has really existed there for a short time or its previous existence was unrecognized. The earlier accounts would indicate that this disease was confined to the sea coast and near the mouths of great rivers, but, quite naturally, these regions came first under the observation of scientific men and it was not until later that explorations into the interior enabled the recognition of its existence in these parts.

As we have stated, the word indicating this disease is found in Chinese literature written 2500 B.C. We infer that the disease existed at that time. Within the past 100 years beriberi has certainly decreased in China and at the present time it is a comparatively rare disease in that country; on the other hand, beriberi, old as it is in Japan, has recently apparently extended from the coast far into the interior and is also found in Formosa and Sakhalin. It has been found as far north in the Japanese Empire as Hakodad on the Yezo Island. At the time of the American occupation this disease was widely prevalent in the Philippine Islands, but within recent years it has been greatly reduced by attention to diet. The Dutch found it in the East Indies and it was in these Islands that the disease first came under the observation and study of European physicians. It is only occasionally seen at Batavia. In 1841 there appears to have been an epidemic involving, according to van Leent, 8000 people at Passaroeang. Its appearance in Borneo is said to date from an epidemic on a Dutch ship-of-war at Padang in 1851. It is said to be quite frequent in northern Borneo, where it is more prevalent on the east than on the west coast. Dutch writers at one time pronounced it a jungle disease, although it was quite frequent among the coolies who worked on the European plantations. There is scarcely any doubt that beriberi in some localities in the East Indies has been frequently confounded with dysentery, hookworm disease, and malaria. In Sumatra beriberi has appeared from time to time in epidemic form and is probably at all times endemic. During the war in Acheen the Dutch

troops suffered severely from beriberi, and it is reported as endemic among the natives in the Lampong States. In the neighboring Island of Banca, separated from Sumatra by the Straits of Banca, with a population of about 60,000, beriberi is frequently observed, especially in the mining population. It is reported that in the Celebes and in the Islands of the Molucca Group, this disease has greatly decreased. Beriberi is reported as endemic in New Guinea. Up to the present time it apparently is rare in Australia, although a few cases have been reported on the west coast and on the southeast coast near Sydney. At one time it was common throughout the Straits settlements, though in recent years it has been reported only from prisons and asylums. In India, beriberi was first studied on that part of the coast of the Madras Presidency, extending from Ganjam to Masulipatam, known as the Circars. It was in this region that Malcolmson made his observations. At that time beriberi was found only within a few miles of the coast, or, more properly speaking, it rapidly decreased as one passed from the coast to the interior. In Lower Bengal, beriberi became epidemic for the first time at Calcutta in 1879. Macleod, at that time health officer of Calcutta, made a report upon this epidemic. He stated that it appeared in scattered houses, but, as a rule, several or all the members of a household were seized, single cases in a family being exceptional. The attacks occurred simultaneously or in rapid succession, as if due to a common cause. The death rate was high and the average duration of the disease was about two months. In most instances death was sudden and those who recovered were left in a greatly enfeebled condition. There have been sporadic cases in both German and British East Africa, in the Congo Free State, in Gambia on the west coast, and at Durban on the coast northeast of the Cape of Good Hope. So far as we know, the greater part of Africa, Asia Minor, Siberia, and the whole of Europe, have remained free from this disease.

There is some doubt as to just when and where beriberi first appeared in the Western Hemisphere. It was not until 1866 that it was recognized in Brazil in the province of Bahia, although some Brazilian authorities claim there had been epidemics of it in their country as early as 1825. Since its recognition in 1866, investigation has shown that it is widely distributed and quite prevalent over the greater part of eastern Brazil, and cases have been reported in that country as far west as the Andes. So far as we know, it has not been observed west of the Andes in South America. It has been seen in the West Indies, especially in Cuba, since the early seventies; indeed, in 1873 an epidemic, with a fatality of from 60 to 75 per cent, was reported among the negroes on two plantations near Palmira. It is said to have shown itself for the first time in Cayenne

in 1865. An epidemic among coolies was reported on this Island in 1877. Recently it has been reported in Labrador among those who live on white flour and fish.

Braddon thinks that the appearance of beriberi in Brazil resulted from the opening up of the ports of that country to the trade of the world and was due to the importation of rice. This view is supported by certain Brazilian physicians, notably F  ris and Azevedo, who say that the spread of beriberi in Brazil has been closely associated with the greater and more extensive use of imported rice as a food.

During the World War both beriberi and scurvy became quite serious in the British Forces in Mesopotamia. A special report on beriberi in the Mesopotamian Forces has been made by Sprawson, who concludes as follows:

“The disease called beriberi is a syndrome which may arise from various causes under different circumstances. One class of cases is not due to a food deficiency; but appears to result from an infection. Other cases are due to a vitamin deficiency in the food; this takes a few months to operate in a previously healthy subject and may be called ‘primary beriberi.’ In yet another class the syndrome arises apparently from the effect of some depressing influence or secondary infection on a subject previously rendered susceptible to the disease. These cases may be considered to have been suffering from ‘latent beriberi.’ In all classes the clinical appearance is approximately the same, there being differences only in the relative frequency of various manifestations in the three groups.”

Sprawson says that the idea that beriberi is due to food deficiency has been too dogmatically stated. He refers to the experiments of McCarrison, who claims to have induced polyneuritis gallinarum in birds by infecting them with *Bacillus suipestifer* while they were fed an abundance of mixed grains. In our opinion, this is not convincing. Every student of this disease must admit that grain need not be polished in order to be deprived of its antiberiberic constituent. This disease must have existed before rice polishing came into general use. It should be borne in mind that the antiberiberic substance, whatever it may be, is freely soluble in water and it may be washed out of whole grain and in this way, partially at least, be removed. In reading Sprawson’s paper we find that whenever all the facts are given, the disease can be accounted for by a food deficiency. A ship with 81 men on board, consisting of Europeans, Hindoos, Mohammedans, and Goanese, after six months developed 17 cases of beriberi. There were no cases among the Europeans, 21 in number, and none among the Goanese, 12 in number. Men of both these nationalities ate European rations. Among 28 Hindoos, 14, and among 20 Mohammedans, 3, developed the disease. Sprawson makes the following statement concerning this outbreak on the ship:

“The lower morbidity amongst the Mohammedans is probably because ten days previous to the medical inquiry the captain of the ship read that the disease was

due to food deficiency, and then tried to put the Indian crew on European rations. The Hindoos, however, refused to take them and kept to their former food. The Mohammedans had no scruples. Previously to that time both Hindoos and Mohammedans had been on the same rations. These rations on examination, though abundant in quantity, were evidently deficient in antiberiberic vitamins. The rice was of the polished or Rangoon variety. The flour was white (i. e., not whole meal); it was also weevily. The dhal (a lentil with coat and rich in antiscorbutics), which might have supplied the defects of the rice, was very dirty, containing many moth eggs and maggots. These defects were remedied in various ways, and the captain of the ship wrote some months later that he had had no further cases of beriberi."

In these instances, Sprawson admits that the disease was clearly due to a food deficiency. It is true, according to Sprawson's report, that in the Mesopotamian Army there were some cases diagnosed as beriberi among Europeans, but he fails to give an exact statement of the quality and quantity of the food served these men. No doubt other forms of neuritis have been diagnosed as beriberi. It is likewise not doubtful that Europeans may have this disease without eating polished rice, but before we can form any opinion as to the influence of food in these cases we must know more about the correctness of the diagnosis and have greater detail concerning both the quantity and quality of the food.

At the siege of Kut-el-Amara, which lasted from December 4, 1915, to April 29, 1916,—148 days—both beriberi and scurvy developed among the besieged troops. Beriberi was practically confined to the Europeans, while scurvy appeared only among the Indians. The beriberi was of severe type, of the wet or dropsical variety, with a few acute cases, one dying within thirty-six hours and another within three days after admission. In 40 per cent there was abdominal dropsy; in 50 per cent, pulmonary edema; and in 10 per cent, dropsy of the pericardium, with cardiac dyspnea; all of the last named cases died. The European troops ate white bread and horse flesh, while the Indians subsisted almost entirely upon atta (a coarse wheat flour, rich in antiberiberic substances) or barley flour. Chick and Hume, after studying these data, say:

"There is no doubt that the British troops were protected from scurvy by the ample daily rations of meat or horse flesh served out to them throughout the siege. The Indian soldiers while protected from beriberi by the nature of their cereal ration, failed in many cases to obtain a sufficient supply of antiscorbutic vitamin, owing to their refusal to eat meat."

Hehir states that about the end of February, herbs, shrubs, and grasses sprang up and to his surprise, although the men were on a barely subsistent diet, the use of some three ounces of green herbs per day, per man, collected from the plains, cured the scurvy. He is of the opinion that fresh meat alone, without vegetables, will not indefinitely postpone scurvy, although it may delay its appearance. The Gurkha, who ate

meat in almost the same quantity as the British soldier, suffered to some extent from scurvy.

Shorten and Roy report that sun-dried carrots, spinach, cabbage, and onions retain in full their antiberiberic properties and that cabbage, carrots, and onions subjected to the same process retain to some extent their antiscorbutic properties, which disappear wholly from spinach.

Climatic and Seasonal Influences.—As our statements concerning the geographical distribution of beriberi show, this disease is most prevalent in tropical and subtropical countries, but we have already called attention to the fact that in the Japanese Empire it has been observed on the Island of Yezo which has a climate corresponding to the temperate zone of Europe and America. Hirsch, in discussing this subject, calls attention to the fact that in many parts of the tropics this disease has never been seen and that outbreaks on board ships in high latitudes have been reported. From this he concludes that climate itself does not determine the endemic or epidemic existence of the disease; indeed, it is quite certain that climate is not a factor except insofar as it determines the character of the food. We have also called attention to the early opinion that beriberi was confined to the sea coast, and we have shown that this has proved to be error when further penetration of the interior has given opportunity for more extended observation. There is but little doubt that in some countries beriberi has been confounded with malarial fevers. While it is true that the area of the earth traversed by beriberi lines is in large part also malarious, it is equally true that even in these areas there are sections where one of these diseases prevails to the complete exclusion of the other. The most malarial districts of India are most free from beriberi and certain sections in which beriberi is common are wholly free from malaria. So far as climate is concerned, including swampiness of ground and presence of anopheles, there is no relation between the two diseases.

It has been a matter of early and frequently repeated observation, that the dark races are more frequently subject to beriberi than are Europeans. According to Simmons, Europeans and Americans in Japan are very rarely attacked by this disease. Anderson states that not a case of beriberi occurred among the French and English soldiers stationed at Yokohama. Brazilian physicians report this disease in all classes in their country. Féris says that among his people it shows no respect for wealth or social position, but he points out that it is rare among visitors. It is worthy of note that from time to time, extending back more than 100 years, students of this disease have called attention to the observation that a certain period of residence in a locality where beriberi exists

is essential to the development of the disease. Nearly 100 years ago Calhoun wrote:

“It appears that a stay for some months at the station is almost essential for the production of the disease, and that the greatest predisposition to it exists when troops have been about eight or twelve months in the settlement.”

Some years ago Simmons observed that Japanese coming from the interior, where the disease at that time was rare, resided on the coast, where it was frequent, for months before they showed symptoms of the disease. Baelz makes a similar statement, inasmuch as he says that a residence in the locality of from a few months to a year is necessary in order to predispose an immigrant to the disease. Since it has been demonstrated that beriberi is a nutritional disease and that persistence in certain diets for considerable periods of time is necessary to induce it, all these statements are easily understood.

One of the oldest theories concerning beriberi assumed that it is a form of rheumatism and that it is brought about by exposure to marked fluctuations in temperature, and especially when these changes are accompanied by wet weather. The supposition of the relation of beriberi to rheumatism was probably suggested by the burning of the soles of the feet, which is a common symptom in chronic cases and by the peculiarities in gait which characterize the disease. It is interesting to note that Malcolmson wrote his treatise on beriberi because two prizes were offered, one for an essay on beriberi and one for an essay on rheumatism, or “burning of the feet.” Malcolmson was awarded both prizes and the two essays were published in one volume; indeed, the essay on “burning of the feet” is more interesting and, in our opinion, a more valuable contribution to our knowledge of nutritional disorders than the essay on beriberi. Malcolmson was apparently halfway convinced of the relation between beriberi and “burning of the feet.” In one place he wrote:

“Both, then appear to depend on an affection of the nerves, and their occurring together would suggest that they are modifications of the same disease; which is further supported, by the fatal cases exhibiting many of the graver symptoms of beriberi. The evidence of an occasional correspondence in some of the symptoms and even of the appearances on dissection, are however by no means sufficient to identify two diseases, as these must often run into each other, if similar parts are affected.”

“Burning of the feet” occurred among native troops in the Burmese War and soon thereafter. The ration of these men consisted of rice, two ounces of ghee (not always issued), a little salt fish, and spices. Those who complained of “burning of the feet” were at first regarded as malingerers, but Malcolmson showed that this was unjust and found that the men were best treated without medicine, by rest, and with the supply of a more liberal diet.

Dietetic Influence.—In most beriberi countries, rice is the most important vegetable food; indeed, taking the world over, there are probably more people depending upon this grain for their principal carbohydrate supply than of those who rely chiefly upon wheat, rye, or potatoes. It is said that in Asia alone at least 400,000,000 Japanese, Chinese, Malays, and Indians depend upon rice for their staple diet, and among many of these the food consists largely of this grain. Rice keeps better when the pericarp (silver skin) has been removed. In most countries where this is the staple article of diet the pericarp is more or less completely removed before the grain goes to the market. As thus prepared, it is known variously as "white rice," "polished rice," "scoured rice," or, "highly-milled rice." When the pericarp is not removed the preparations go under the names "red rice," "unpolished rice," "medium-milled rice," and "under-milled rice." In 1896 Eykman, of the Dutch East Indian Service, fed chickens and pigeons upon an exclusive diet of polished rice and found that these animals after a variable period of time, from a few weeks to a few months, developed a general paralysis, which has since been known as polyneuritis gallinarum or the polyneuritis of birds. Eykman was so struck with the similarity between this disease and the beriberi of man that he decided to extend his experimentation to human beings. There was no scarcity of beriberi in the jails and prisons of the Dutch East Indies and, consequently, there was abundant material at hand for this experimentation.

In some of these institutions the inmates were fed upon rice which still retained at least 75 per cent of the pericarp or the so-called silver skin. Of 37 prisoners kept upon this diet, only one, or 2.7 per cent, developed beriberi. In a second group of 51 who were fed upon rice from which at least 75 per cent of this layer had been removed, 36, or 70.6 per cent, developed beriberi. In a third group of 13 who were fed upon a mixture of these two kinds of rice, 6, or 46.1 per cent, developed the disease. Eykman made a close study of the local conditions which might possibly be of influence and came to the conclusion that in all probability the differences in diet were wholly responsible for the marked differences in the numbers developing the disease. Later, on his return to Holland, Eykman continued his experimental investigations and, although his results were not constantly uniform and he met with many setbacks on account of the development of intercurrent diseases among his animals, his suspicion that the polyneuritis in birds is wholly explainable by diet seemed justified. He found that he could induce polyneuritis in birds by feeding them on polished rice and that he could then cure them by adding to their food the pericarp which had been removed, or by means of an extract of the pericarp. When whole rice was kept

for two hours at 125° C. in a sterilizer and chickens were fed on this preparation they developed polyneuritis; in other words, superheated steam when continued for two hours destroys the antiberiberic substance, whatever it may be, in whole rice. Heating for the same time to 115° C. also destroys, partially at least, the antiberiberic substance. Ordinary cooking at 100° C. has no destructive action upon this constituent of the food. Extending his investigations, he found that subjection for a long time to the high temperatures mentioned above, destroys the antiberiberic substance or substances in rye, oats, and barley, as well as in rice. Eykman and his followers claim it has been demonstrated that rice may produce beriberi and that its activity in this direction varies directly with the extent to which the pericarp or silver skin has been removed.

Eykman came to the conclusion that polished rice contains a substance, a poison or a toxin, which has a deleterious effect upon the nervous system and that the pericarp contains a body which antidotes or neutralizes the poison. He found that the protective substance can be extracted from the bran or polishings with water, that it is dialyzable, and that it is not precipitated by alcohol; indeed, it is soluble in both water and 95 per cent alcohol. It is destroyed by a temperature of 130° C. and its active properties are reduced by prolonged exposure to a temperature as low as 115° C. and possibly somewhat affected at slightly lower temperatures. Funk took up the study of this so-called antiberiberic vitamin and he has been followed by hosts of workers in various parts of the world, but, so far, the chemistry of this substance has eluded every attempt to solve the problem satisfactorily. At one time Funk went so far as to propose a chemical formula for this vitamin, by which he makes it a base belonging to the pyrimidin group. He thinks that this body is essential to the normal metabolism of nervous tissue and that when it is not present, changes in these tissues develop and from these changes the signs and symptoms of beriberi result.

Funk and Douglas have suggested that beriberi may be due to degenerative changes in the endocrinal glands. They found this claim upon the examination of eight beriberic pigeons and state that while the thymus in normal pigeons is a long organ extending in a chain of glands through the whole length of both sides of the neck, in beriberic patients no tissue that could be identified as thymus was found. In the glandular portion of the pituitaries there were marked deviations from the normal, the acinar arrangement being lost and the cells showing degeneration. In two of the birds there was marked degeneration of the cells in the thyroid. In the six female birds the ovaries were much diminished in size, while in two male birds the testes were greatly atrophied. In the

majority of the birds there were some slight degenerative changes in both cortical and chromaffin cells of the suprarenals. It must be admitted that this work is not altogether convincing, because we are not sufficiently familiar with the histology of these organs in pigeons, either in the normal state or when suffering from other diseases.

Fraser and Stanton hold that the smaller the percentage of phosphorus in a diet the greater is its potency in producing beriberi in man or neuritis in birds. Schaumann follows along the same line and draws the inference that the substances in food which are protective against beriberi are probably organic compounds of phosphorus. Simpson and Edie, after a review of this subject and a report of some investigations of their own, state their conclusions as follows:

“(1) Foodstuffs which lead to the development of polyn neuritis in animals are characterized by a low content of phosphorus or of certain organic compounds of phosphorus. This may be either fundamental or be caused by artificial processes. (2) Animals are not protected from the ill effects caused by such diets by the addition thereto of proteins, inorganic salts, inorganic phosphates, or the synthetic organic compounds of phosphorus (calcium glycerophosphate or albumen-metaphosphate). (3) The addition of certain substances, rich in organic phosphorus, to such diets exercises both a protective and a curative effect. Yeast, rice meal, wheat bran, peas, Katjang beans, and testicular extracts are the chief substances with this power. Carnivora and herbivora, however, react rather differently to testicular extract; the former are completely protected, the latter only in a less degree. (4) Artificially separated organic phosphorus compounds of various kinds, prepared from these natural protective substances, exercise only a moderate and transient influence. Such compounds include yeast, nucleic acid, phytin-like compounds from Katjang, phytin from rice meal, and possibly certain phosphatides. (5) Apparently the protective or curative effect of these substances is dependent not on any one of their organic compounds of phosphorus, but on the collective effect of a number of these. Animals do not apparently possess the power of forming the organic phosphorus compounds necessary to their economy from inorganic phosphates by their own metabolism, but are dependent for their provision on the plant world, as they are for other classes of foodstuff (e.g., protein and carbohydrate). (6) The metabolism of phosphorus and nitrogen stand in close relation to one another. (7) Spontaneous or experimental polyn neuritis in animals appears to be a disease of metabolism, attributable to the lack of some specific organic phosphorus compounds whose identity is still uncertain.”

It seems to be generally agreed at present among students of beriberi that a rice which yields less than 0.4 per cent of phosphorus pentoxid is not a safe food. Fraser and Stanton say that they have never known an outbreak of beriberi to be caused by a rice which yields more than 0.26 per cent of phosphorus pentoxid and that rices containing not less than 0.4 per cent of this constituent are effective in preventing the continuance of the disease. Strong and Crowell caused beriberi by feeding men with rice which contained 0.37 per cent of phosphorus pentoxid when the rice formed the staple article and there was but little

variety in the diet. In 1912 Heiser suggested that the Philippine Government tax rice containing less than 0.4 per cent of phosphorus pentoxid. Fraser and Stanton found that on an average unpolished rice contains 0.54 per cent of phosphorus pentoxid, and Aron found that unpolished rice in the Philippine Islands contains 0.557 of phosphorus pentoxid. Strong and Crowell suggest that a more thorough study of the amount of this constituent in rice be made before a legal limit is determined. Chamberlain thinks it probable that the potassium compounds in the pericarp play an important part in this matter.

A great many practical experiments have been made by excluding polished rice from the diet. It was the boast of Takaki that he freed the Japanese Navy from beriberi by a change in the ration. Up to 1883 this disease involved one-fourth of the strength of the Japanese Navy. In 1884, through the influence of Takaki, the ration was changed and a larger proportion of nitrogenous food was provided. In 1885 there were only 41 cases, and in 1886 only three cases, of beriberi. Since that time it is claimed that this disease has been eliminated from the Japanese Navy. It is said by Vorderman that among 96,530 prisoners in Java who were fed chiefly with rice from which not more than twenty-five per cent of the pericarp had been removed, only 9, or 0.009 per cent, developed beriberi, while among 150,226 prisoners fed with rice which contained not more than twenty-five per cent of the pericarp, 420, or 0.28 per cent, had beriberi. This investigator concludes that there is an undeniable connection between the consumption of polished rice and the prevalence of this disease. In 1901 Roefsema cared for an epidemic of beriberi among coolies at the coaling station at Sabang, Sumatra. No improvement followed when he added meat to the food, but the epidemic soon ended when the sick were fed on Katjang peas. Similar observation was made by Jonge in an insane asylum at Buitenzorg. After an experience of five years with beriberi, Braddon came to the conclusion that this disease is not an infection but a food poisoning, the cause of which lies in the nature of the grain. In places, where rice eaters and nonrice eaters live side by side, sharing in common the chance of infection, beriberi attacked only rice eaters, never the non-rice eaters. Fletcher found in an insane asylum in the East Indies that there were 34 cases of beriberi among 120 persons fed upon polished rice, with 18 deaths; while among 123 patients fed upon unpolished rice there were only two cases, both of whom had the disease on admission. Fales, studying beriberi in the Bilibid Prison in Manila, came to the conclusion that both this disease and scurvy are due to a lack of fresh vegetables. He attributed the diet deficiency to the small amount of potassium carbonate in the polished rice. Ellis, studying this disease in a Singapore insane asylum, states that since only unpolished rice has been used as a food there has been no recurrence of the disease, although there were formerly many

outbreaks. Fraser and Stanton made what appears to have been rather a crucial test. They took 300 Javanese laborers who were employed on road construction and divided them into two camps. Those in one camp had polished rice, while those in the other had unpolished rice. The disease appeared only in those fed upon polished rice. The diets in the two camps were interchanged, with a reversal after a time in the disease condition. They state:

“Removal of patients suffering from beriberi from one place to another did not influence the progress of the disease and removal of entire parties from the place where the disease had occurred did not influence the progress of the outbreak so long as they continued on white rice. These experiments suggest, although they do not prove, that place *per se* or considered as a nidus of infection has no influence upon the development of beriberi.”

Strong and Crowell made a carefully guarded experiment on prisoners in the Bilbid Prison and came to the following conclusion:

“It is evident that among the individuals comprising our experiments beriberi was produced only by means of the diet, and that the disease has, therefore, a true dietetic causation. It is further evident from our experiments that beriberi develops owing to the absence of some substance or substances in the diet necessary for the normal physiological processes of the body. Without the supply of such substances in the food, beriberi results. Such a substance or substances are evidently present in red rice and in rice polishings and also in small amount in the alcoholic extract of rice polishings, and when these articles are added to what would appear to be an otherwise physiologically proper diet, they usually prevent the development of the symptoms of the disease. In some instances, however, even when these substances are constituents of the diet, when the diet is without variation and composed of very few articles, and the individual suffers from loss of appetite and the assimilative functions appear to be poor and he loses markedly in weight, symptoms of beriberi may develop in such individuals. However, such symptoms may be dispersed by causing a variation in the diet by the addition of other nitrogenous substances to it. It is also evident from our experiments that the disease is certainly not an infectious one in the sense which we usually employ this term. The rigid isolation of the prisoners undergoing the test would seem to exclude the possibility of the introduction of an infectious agent through any other individual or by the introduction of any article. * * * It is also noteworthy that the cases of beriberi developed under the most favorable hygienic conditions with exception in regard to diet. It is not probable that the infection could have been introduced with the food, since this was all freshly cooked, and at a temperature at which only a spore-bearing organism would survive. The food was also eaten a very short time after being cooked. Moreover, if the infection had been introduced with the food, the incidence of the disease should have been the same in all of the groups, which it was not. No fermentation of the rice employed occurred either before or after it was cooked, so that it would appear that the action of such bacteria as have been described by Köhlbrugge and by Bréaudat could be excluded. It has been suggested that a diet of white rice predisposes to the disease, since it furnishes a better medium for the development of the specific organism which resides in the intestine of the host, and that the red rice or extract of polishings forms a preventive for the development of such a specific organism. There is no definite evidence of such

an hypothesis and, moreover, the results obtained in our experiment would argue against it, since in two instances at least, distinct symptoms of beriberi were present in individuals who had received these substances in the diet. It cannot be claimed with reason that the resistance of the individuals having been lowered by weakness and loss of weight, the specific organism residing in the intestine of the individual was able to increase and multiply and produce the disease; for in several instances where the loss of weight of the individuals was marked and their general condition poor as was manifested by the occurrence of erosions about the corners of the mouth, sore mouth and tongue, and conjunctivitis, no symptoms of beriberi developed. Indeed, from our experiments there is no evidence of any nature which suggests that beriberi is an infectious disease, and on the contrary the evidence is definite that beriberi in the Philippine Islands is due to the prolonged consumption of a diet which lacks certain substances necessary for the normal physiological needs of the human body."

There are those who still deny the importance of the dietetic factor in the causation of beriberi. Wright, studying the disease in a jail at Kuala Lumpur, holds that beriberi is not due to diet, but is due to infected localities. He states that in this asylum, although the inmates were on the ration provided by Takaki for the Japanese Navy, 49 cases of this disease originated and 123 redeveloped signs of paresis or recontracted the disease during the continuance of the diet. Similar reports have come from Durham, Travers, Daniels, and Montel. It will be seen from this that there is some difference of opinion, as yet, among those who have had opportunity to study this disease as to its causation, but the weight of evidence seems to be in favor of those who hold that beriberi is a nutritional disorder.

In the third edition of his valuable work on tropical diseases, published in 1903, Scheube, who had had experience with beriberi in Japan, wrote that beriberi is an infectious disease and not a nutritional disorder. He gives the following principal reasons for this belief: In the first place, the disease is especially prevalent among lusty, well-nourished, young adults. Secondly, it is most prevalent on the sea coast and near the mouths of great rivers and is rare in the interior. Thirdly, it is seasonal, being most prevalent during the rainy season; and, fourth, the disease has recently extended to countries, the inhabitants of which do not depend upon rice as their staple article of diet. It is quite evident that Scheube had not at that time, although Eykman's work had been published some years previously, comprehended the food deficiency theory. As we have seen, strong, as well as weak people are liable to develop this disease when their food is deficient in antiberiberic properties, and highly-milled wheat may also be deficient in antiberiberic constituents.

So far, the discussion has centered about rice as a staple article of diet. If polished rice may cause this disease, is it not possible that other grains treated in a similar way may have a like effect? A report made by Little

in 1912 concerning beriberi in Newfoundland should be regarded as of great importance. This author writes as follows:

“A great many people here live from hand to mouth, being always on the verge of poverty. There are many who are well satisfied if they have enough flour, tea and molasses to see them through the winter. Agriculture is so discouraging that many never have a vegetable. Game, deer, birds, rabbits, seals, are scarce and getting scarcer. Berries, though abundant in the fall, are hard to gather. Fish is worth more to sell than to eat, for with it flour, which is the cheapest food, is bought. Although there are times of the year when such people get all of these, there are times when they get none of them and those are the times when the physician begins to hear various complaints. These complaints are in many cases vague, in some definite. Such for instance are night-blindness, retention of urine, numbness or cold feelings, tingling in the legs or arms, or across the abdomen or mouth, feelings of water running up and down under the skin, etc. These are the paresthesias, the functional nervous troubles which are the prodromal stage of beriberi. They are very common. Let the vessel get home, or the spring come, the ice break up, navigation open, and a more varied diet be taken, and they disappear. But let an added burden be thrown on the economy, whether it be pregnancy, a wetting and chill or a cold; add the squalor and discomfort, dirt and bad air of one of the air-tight overheated cottages the natives live in, increased by the neglect caused by their own undermined health, then you will see the condition advancing sometimes very rapidly to the later stages of sensory and motor paralysis, with affection of the peripheral or special nerves, involvement of the heart, or any other organ, edema, etc., and sometimes death. I have seen the advance into complete helplessness of a patient who complained only of night-blindness with paresthesias, anesthetics and paralysis. I have seen the same patient, put on a diet of whole-wheat flour, beans and peas, get perfectly well in two months. I have taken into hospital patient after patient advancing from the functional stage of symptoms into the paralyzed, and, by giving a full diet with whole-wheat bread, beans, potatoes, macaroni and fresh meat, had them well in two weeks. I see two to three cases a day now, and during the last two months have taken in the worst ones and cured the patients in two weeks. On one part of our coast where beriberi has been most common, in the fall of 1910 a large vessel went ashore from which whole-wheat flour was unloaded to lighten her. The natives got the flour and there has not been a case there since, nor any of the functional symptoms. The ‘old staggers’ of this country who remember the days when ‘brown flour’ was the diet, say that this trouble was unknown among them.”

In 1903 Young reported that during the past five years he had met with many cases of beriberi in the neighborhood of Abbeville, La. He stated that in this district there had been not less than 40 cases and in all of these the patient was a heavy eater of rice.

It is stated in an Italian journal, also in the *Journal of Tropical Medicine*, (Sept. 1, 1905, p. 270), that there were 40 cases of beriberi with three deaths among the Filipinos present at the St. Louis Exposition in 1904. In 1895 Bondurant reported between 20 and 30 cases in the State Insane Asylum at Tuscaloosa, Ala., and later other cases in an insane asylum in Arkansas. These may or may not have been correctly diagnosed. On reviewing Bondurant's report, Braddon concludes that if it were beriberi it was of modified type. It is exactly this that we must look for in this

country. It is highly improbable that beriberi developing in this country would in every particular present an exact reproduction of the symptoms as seen in this disease in oriental countries. For a time Caverley was half persuaded that the cases which he reported as poliomyelitis in the outbreak near Rutland, Vt., in 1894, were due to beriberi, but this keen observer soon became convinced that his original diagnosis was correct, and so it has proved to be.

The U. S. Mortality Statistics show 78 deaths reported as due to beriberi from 1911 to 1919, distributed as follows: 1911, 7; 1912, 12; 1913, 11; 1914, 5; 1915, 6; 1916, 6; 1917, 15; 1918, 11; 1919, 5. In 1918 there were 5 deaths in California, 4 in Washington, and 2 in New York. In 1919 there were 4 in California, and 1 in Tennessee. Where the disease was acquired in these cases we are not informed, nor can we guarantee correctness of diagnosis.

It is of importance that we make some inquiry as to the content of anti-beriberic substance in foods other than rice. White bread is quite certainly lacking in this substance. Holst found that animals fed on wheat bread developed neuritis, while those fed on rye bread did not. Sailors on Norwegian sailing ships began to develop beriberi in 1894, the disease having been unknown among these people before that time. This corresponds with a change of their ration from rye bread to wheat bread, the wheat bread being served in the form of hard-tack made from over-milled wheat flour. Potatoes contain appreciable quantities of the anti-beriberic substance; at least, Eykman found that chickens fed entirely on potatoes do not develop polyneuritis. This is confirmed by the fact that this disease has, so far as we know, never appeared among Irish peasants, even when they have been compelled to live chiefly on potatoes. No one, however, has ever tried a diet consisting of polished rice and potatoes or white flour and potatoes. It remains to be determined whether or not the anti-beriberic substance is present in potatoes in sufficient quantity to make up for its absence from polished rice and white bread. It has been quite generally found that peas and beans contain satisfactory amounts of the anti-beriberic substance. The content of this body in meat is apparently small. Vedder and Clark state that both meat and potatoes are more protective cooked than when eaten raw. This is contrary to what one would naturally expect and a more thorough investigation should be made along these lines.

We think it rather unfortunate that beriberi has been so closely associated in the literature with rice. In part, we think this is due to a superficial reading of some of the classical works on this disease. For instance, in 1907 Braddon wrote:

“(1) That in places where beriberi is endemic and in communities in which it prevails, only those who eat rice are attacked; those who eat no rice escape. (2) Among rice eaters in endemic areas, or during epidemics, those only who eat certain

—uncured and stale—sorts of rice suffer, those who eat only other—cured or fresh—sorts escape. (3) In epidemics as with persons where such uncured rice is consumed, the extent (prevalence and severity) of the disease varies directly with the quantity eaten, absolutely and relatively. (4) The disease persists when the sort of rice eaten when it was acquired, continues to be used and disappears when this is changed.”

The careless reader no doubt concludes that rice, and this food only, may cause beriberi; but a more careful and wider reading of Braddon's book shows that he was even at that time quite conscious of the fact that other grains, as well as rice, might be concerned in the causation of this disease; in fact, he says this plainly and at times states that beriberi is due to poisoning with grain. He also calls attention to the fact that travelers going into countries where the disease is unknown, who carry with them their special food and adhere to it, may develop the disease. He says that death is in the pot.

The question has arisen whether or not any restriction should be placed upon the sale and use of polished rice in this country. The natural answer is that our food is so abundant and so varied that there is no danger of our being afflicted with such a disease as beriberi. We are not sure that the matter should be treated in this way, but, in our opinion, we are in more danger of suffering, certainly in the northern part of the United States, from fine wheat flour and the bread made from it than we are from polished rice. In every case of neuritis the physician should inquire closely into the dietetic habits of his patient, and we would not be surprised if it came to pass that many cases of this disease are due to dietetic error. The fact that the patient is well-to-do and lives liberally so far as food is concerned should not debar the physician from making his inquiries. It should be borne in mind that beriberi is not due to too little food, but to the kind of food, and especially to the processes to which food has been subjected before it is consumed.

We cannot too fully emphasize the fact that beriberi is a food-deficiency disease and that it is quite as likely to occur in the families of the well-to-do as in those of the poor. In the selection of our foods it is custom rather than taste and flavor or good sense that leads us. In well-to-do families only wheat bread made from the finest flour is used. The humbler neighbors copy this fashion and after a while it comes about that everybody demands that wheat flour must not only have all the bran excluded, but it must be bleached in order to please the sight. Finally, it comes about that to buy any other than the whitest wheat flour is to acknowledge that one is deficient both in culture and in purse. We are just beginning to realize, in the examinations of school children that are now being made quite extensively, that undernourished children come in astonishingly large numbers from well-to-do families; indeed, the children of physicians

not infrequently show that their fathers, either through ignorance or indifference, fail to properly supervise their food. It should be plainly understood that, according to our best present-day information concerning the causation of beriberi and scurvy, these diseases are not due to the *presence* in the food of harmful substances, but are due to the *absence* from the food of certain essential nutritional elements. Manufacturing pharmacists are already offering supplies of vitamins to physicians and trying to make money out of our recently acquired knowledge concerning the food-deficiency diseases. It may be plainly stated that such preparations are not to be used and are not needed. The proper thing to do is to give the natural food containing the vitamin.

It is well to bear in mind that neuritis is not the only symptom of beriberi in man or of polyneuritis in birds. As we have seen, beriberi in man may be accompanied by edema or it may be free from this symptom. In the neuritis of birds, edema, so far as we know, has never been observed. In both man and birds, however, there is loss of weight, and this is quite independent of the amount of food and the presence of proper quantities of protein, fats, and carbohydrates. In experimental polyneuritis the loss in weight is quite variable and does not always correspond in degree to the development and extent of the neuritis. Studying this problem, Vedder and Clark suggest that rice polishings and other foods contain two substances that are essential to proper metabolism. One of these is a neuritis preventing substance, while the other prevents the loss in weight, prostration, and cardiac failure. This, however, is a matter of speculation. It is not necessary to assume that the lack of antiberiberic substance leads directly to abnormal metabolism in the peripheral nerves. It may affect these organs indirectly by its more direct effect upon other tissues in the body.

Infantile Beriberi.—In 1888 Hirota began to report cases of infantile beriberi and since that time he has continued the study of this disease. Since the American occupation of the Philippines, both native and American physicians have contributed valuable information on this subject. In Manila the disease is known among the natives under the names of taon, taol, and suba. In the United States and in European countries the infantile death rate is much higher among artificially fed infants than among those breast fed, while in the Philippines the opposite is true. In 1910 McLaughlin and Andrews wrote:

“In the Philippines the mortality is greatest among breast-fed children, possibly because of the poor quality of the mother’s milk. The latter is probably deleterious by reason of what it lacks rather than because of any harmful constituent. The average Filipino mother is in poor physical condition, many of them are beriberic and subsist upon a diet favorable to the production of beriberi. It seems probable that there is an intimate relation between beriberi of infants and a mother’s milk poor in quality and lacking certain necessary elements which are not included in the mother’s dietary. * * * A possible solution of the problem lies in improving

the quality of the mother's milk and encouraging the continuance of the custom of breast-feeding so general among the Filipino poor. The improvement of the physical condition of the Filipino mother and of the quality of her milk is an economic question. Her condition is the result of poverty and therefore insufficient and unsuitable food, especially during the periods of pregnancy and lactation."

Philippine beriberic infants get well if they are taken from their mothers and given proper food, unless they die from some gastrointestinal trouble, which they are likely to do. The proper thing, therefore, is not to take the child from its mother or to deny it breast food, but to supply the mother with proper food. It seems that the poor in the Philippines have an aversion for unpolished rice and demand the polished variety. This is especially true in the city. In the country they prepare their rice daily by pounding it on a stone, and mothers who live upon this preparation do not have beriberic children. In 1912 Andrews made a most interesting experiment. He induced Philippine mothers who were beriberic and who had lost their children, to nurse puppies. The mother continued on the beriberic diet. Andrews states:

"To summarize, all of these puppies showed incoordination and weakness of the extremities, particularly of the hind legs. In all slight degeneration of the peripheral nerves by the Marchi method was demonstrated. All showed edema and anemia of the subcutaneous tissues. These findings agree entirely with those of the infants dying of beriberi. However only one of the puppies showed the dilation and hypertrophy of the right heart which I have regarded as a constant finding in infantile beriberi. In my opinion these experiments furnish, therefore, additional evidence that the condition described as infantile beriberi is due simply and solely to the ingestion of the mothers' milk."

It is interesting to note in this connection that the mother's milk in these cases, as shown by analyses, is quite normal so far as protein, fat, and carbohydrate are concerned. Some of the samples examined were found to be exceedingly rich. This is another indication that beriberi is not due to deficiency in the ordinary foodstuffs, but is due to the lack of the specific antiberiberic substance. Furthermore, it is worthy of note that in at least one sample of the milk examined, the amount of phosphorus pentoxid was nearly double the average found in woman's milk. Andrews states (1912) that fifty per cent of the total deaths of Filipinos in Manila are of infants one year of age and under, and over fifty per cent of these are due to infantile beriberi.

Dr. José Albert informs us that while in 1912 more than one-half the children born in Manila died before they reached one year of age, in 1920 this ratio had fallen to less than one-fifth.

We have referred to the fact that there have been many theories concerning the etiology of beriberi. Some of these are quite obsolete, while many still have their adherents. It may be interesting to merely state some of these theories. (1) It was held by early Dutch observers and some

of the English that this disease is due to morbid substances with which the water and air become impregnated. (2) It was once suggested by Manson that beriberi is due to a place organism which distills a toxin into the air and that the inhalation of such air induces the disease. (3) At one time it was held by certain Japanese physicians that beriberi is due to the eating of certain fish which, especially at certain seasons of the year, are inherently poisonous. (4) It was held by Grims that this disease is due to the ingestion of infected air. (5) Gelbke thought it due to fish infested with trichinae. (6) It was quite widely held at one time that beriberi is a form of pernicious anemia. (7) Some of the early English investigators in India believed that beriberi is a form of rheumatism. (8) Others were convinced that it is a modified scurvy. (9) Ross at one time suggested that it might be due to arsenical poisoning caused by contamination of the grain. (10) Some thought that it might be a carbon monoxid poisoning. (11) It was suggested by Glogner that it is due to a plasmodium. (12) Okata and Kokubo thought they had demonstrated as the causal agent a specific diplococcus. (13) It was held by Braddon that beriberi is due to a specific organism which develops on growing rice. (14) Many careful investigators, Wright, Durham, Travers, Scheube, and others have come to the conclusion that it is due to infected localities. (15) McCarrison at one time believed that beriberi results from infection with *Bacillus suispestifer*. (16) It has been suggested that a diet of polished rice or white flour furnishes a better medium for the development of specific organisms that reside in the alimentary canal. (17) Beriberi has frequently been confounded with hookworm disease, although in many of these instances the two diseases have coexisted in the same individual. (18) At one time it was held by Funk and Douglas that this disease is due to abnormal function in the endocrinal glands. (19) It was on the theory that beriberi is due to an unbalanced diet, too low in nitrogen, that Takaki reduced the prevalence of this disease to practically zero in the Japanese Navy. (20) Eykman held that the disease is due to a specific poison present in polished rice which is neutralized by something in the pericarp. (21) It has been repeatedly suggested, especially by Fraser, Stanton, and Schaumann, that beriberi is due to a deficiency of organic phosphorus content compound. (22) Fales attributed this disease to the inadequate supply of potassium carbonate in polished rice. (23) Sprawson thinks that beriberi etiologically designates at least three distinct diseases, (1) due to an infection, (2) due to a food deficiency, (3) due to some general depressing influence.

In his recent (1921) monograph on deficiency diseases, McCarrison, by experiments on birds, reaches the same conclusions that Sprawson arrived at from his clinical experiences. McCarrison holds that, etiologically, there are three forms of polyneuritis columbarum: (1) Those due solely to avitaminosis; (2) those due to avitaminosis plus infection; (3) those due

solely to the infecting agent. This author finds that inoculation of pigeons with *Bacillus suispestifer* produces polyneuritis, but that the disease appears more promptly and progresses more aggressively when birds are fed upon a vitamin-deficiency food. On the other hand, birds may be protected from the infective type of polyneuritis by proper feeding. McCarrison makes the following general statement:

"I consider that in the presence of avitaminosis, be it complete or partial, infections, capable either of causing polyneuritis themselves or of precipitating the nerve degeneration to which the subjects are predisposed, are liable to occur and to modify the etiological, symptomatic, and morbid anatomical features of this malady. Pathologic agents, of whatever kind, that are capable of further depressing the impaired metabolic resources of the body, and especially that of the endocrin regulators of metabolism, may be excitants of beriberi, and convert a state of potential morbidity into one of actual disease. The organisms need not always be such as will produce polyneuritis on inoculation, although in some instances they may possess this power—as judged by the experience with *Bacillus suispestifer*. Many of those who have practiced in the tropics will be familiar with cases of beriberi occurring as a sequel of dysentery; and while it is possible, even probable in some cases, that the dietaries employed in the treatment of dysentery may be such as to precipitate the onset of beriberi in persons predisposed to it by previous food conditions, yet the further possibility is not to be overlooked that organisms having themselves a specific action on nerve tissue may sometimes be the responsible agents concerned."

It might be well to state the following general rules for the prevention of this disease. (1) Live upon a well-balanced diet. (2) Eat at least once a week one or more of the following foods: milk, eggs, fruit, fresh vegetables, spinach, onions, carrots, and tomatoes. Do not eat too largely of highly-milled grains. (3) Avoid an excess of carbohydrates, especially in the form of polished rice, white flour, sago, cornstarch, macaroni, and cream of wheat. (4) Guard against a monotonous diet; seek variety in food. (5) While an excess of nitrogen in the daily food may not prevent beriberi, a deficiency of nitrogenous substances does favor the development of this disease. (6) Avoid overcrowding, especially in localities where beriberi is endemic.

Bibliography

- ANDREWS, V. L.: *Philippine Jour. Sc.*, 1912, vii, 67.
 ARON, H., AND HOCSON, F.: *Philippine Jour. Sc.*, 1911, vi, 361.
 BONDURANT, E. M.: *New York Med. Jour.* 1897, lxvi.
 BRADDON, W. L.: *The Cause and Prevention of Beriberi*, London, 1907, Rebman.
 CASTELLANI, A., AND CHALMERS, A. J.: *Manual of Tropical Medicine*, 1919.
 CLEMON, F. G.: *The Geography of Disease*, Cambridge, 1903.
 CHAMBERLAIN, W. P.: *Philippine Jour. Sc.*, 1911, vi, 134.
 CHAMBERLAIN, W. P., BLOOMBERGH, H. D., AND KOLBOURNE, E. D.: *Philippine Jour. Sc.*, 1911, vi, 177.
 CHAMBERLAIN, W. P., AND VEDDER, E. B.: *Philippine Jour. Sc.*, 1911, vi, 395; *ibid.*, 1912, vii, 39.
 EYKMAN, C.: *Arch. f. Hygiene*, 1906, lviii, 150; *Virchow's Arch.*, 1897, cxlix, 187.
 FRASER, HENRY, AND STANTON, A. T.: *Philippine Jour. Sc.*, 1910, v, 55.

- FUNK, C.: Die Vitamine, Wiesbaden, 1914.
- GREIG, E. D. W.: Indian Jour. Med. Res. 1918, vi, 143.
- HEHIR, P.: Indian Jour. Med. Res., Special Indian Science Congress Number, 1919, p. 44.
- HEISER, VICTOR G.: Philippine Jour. Sc., 1911, vi, 229.
- HIRSCH, A.: Geographical and Historical Pathology, London, 1885.
- LITTLE, J. M.: Jour. Am. Med. Assn., 1912, lviii, 2029.
- MALCOLMSON, J. G.: A Practical Essay on the History and Treatment of Beriberi, Madras, 1835.
- MCCOLLUM, E. V.: Oxford Med., 1919., i, 43.
- SCHEUBE, B.: Die Krankheiten der Warmen Länder, Jena, 1903.
- SHORTEN, J. A., AND ROY, C.: Indian Jour. Med. Res., Special Indian Science Congress Number, 1919, p. 60.
- STRONG, R. P., AND CROWELL, B. C.: Philippine Jour. Sc., 1912, vii, 271.
- VEDDER, E. B.: Philippine Jour. Sc., 1912, vii, 415.
- VEDDER, E. B., AND CLARK, E.: Philippine Jour. Sc., 1912, vii, 423.
- YOUNG, F. F.: Jour. Am. Med. Assn., 1903, i, 111.

CHAPTER V

PELLAGRA

Description.—Pellagra, from the Italian words, pelle (skin) and agra (rough), is a chronic, wasting, endemic disease, exhibiting marked skin lesions accompanied by digestive disturbances and developing nervous abnormalities which frequently terminate in insanity. It is a recurrent disease with seasonable exacerbations, most marked in the spring of the year. It is most prevalent among peoples who subsist largely upon unbalanced diets in which proteins, especially animal proteins, are deficient.

History.—The first recorded recognition of this disease was published by a Spanish physician, Casal, who observed and described it as it existed in the province of Asturia in northwestern Spain for the 30 years following 1730. Casal described this disease under the name “mal de la rosa,” and called attention to the fact that Indian corn or maize was a staple article of diet among those affected. In 1771 the Italian physician, Frapolli, wrote a monograph on this disease and gave it the name which it still bears. From that time up to the present Italian medical literature has been replete with contributions founded upon observations of those suffering from pellagra. In 1818 it was observed in the province of Gascony in France. Here, as in Spain and Italy, it followed the introduction of maize as a food. It is claimed that it continued in France as long as maize was so used and that it gradually disappeared as the use of this food was discontinued. In 1830 it was first reported in Roumania. It is probable that in each of these countries the disease had existed and had become endemic before it was recognized and reported. In 1875 it was detected on the Island of Corfu, and in 1888 in Bukowina and in Hungary. About the same time it was found to be quite widely distributed over Austria, especially in those provinces inhabited by Roumanians. In 1894 it became quite widely disseminated throughout the Russian province of Bessarabia, also largely inhabited by Roumanians. In 1892 its occurrence in Mexico was first announced, and a few years later it had become quite common in Yucatan. In 1902, Harris, of Atlanta, reported a case of hookworm disease in an individual presenting typical symptoms of pellagra. This did not attract wide attention, and the physicians of this country did not become aware of the extensive prevalence of pellagra in the southern states until 1906, when it was detected by Searcy in the Alabama Asylum for Negroes.

Babcock, medical superintendent of an insane asylum in South Carolina, took up the matter and found in his institution a number of cases of the disease. Furthermore, going back over the records of the institution he satisfied himself that pellagra dates back to the time of the establishment of that asylum in 1828. However, as Harris points out, skin lesions and intestinal disturbances among the insane are so common and so varied as to justify some hesitation in accepting this evidence concerning the early existence of pellagra in this country.

Etiology.—The first question that naturally arises is that of the transmissibility from person to person of the disease. Italian physicians have made many contributions upon this subject, and from time to time the discovery of the specific infecting organism has been announced. The literature is immense, but it is unnecessary to even abstract it because no claim to the discovery of a causal organism has stood the test of time. Every excretion, secretion, and tissue of pellagrins has been introduced into monkeys of different species in every conceivable way, and in no instance has pellagra resulted. Moreover, experiments of this kind have not been confined to monkeys, but have found numerous volunteers among students and experimenters who have submitted themselves to such inoculations, and the result has been uniformly negative. So far as the evidence goes up to the present time (1922), there is absolutely no justifiable support of the theory that pellagra is due to infection of any kind, either bacterial or protozoal. This theory, therefore, can be dismissed for the present at least.

The statements of Roberts concerning the nontransmission of this disease may be condensed as follows: (1) It is a rural disease and although many pellagrins visit the city, the urban population is not infected. (2) In large families it often happens that only one or two are affected. (3) There is no recorded case in which physician or nurse in constant attendance on pellagrins has acquired this disease. (4) In Italy pellagrous women frequently serve as wet nurses without harm to the child.

Early in the history of this disease it was suggested, as has been of almost all epidemic diseases, that it results from a miasm. At first, this was only an indefinite theory, but even in this form it was long ago discarded by the more intelligent and observant Italian physicians. In 1910 the insect-borne theory in more concrete form was advanced by Sambon, an English physician, who, on a hurried visit to Italy, announced that he had discovered that pellagra is transmitted by a small gnat belonging to the genus *Simulium*. Few experienced pellagrologists have accepted this announcement made by Sambon, and some, with more or less reason, have treated the proponent of this idea with severe

criticism, as is shown by the following quotations. Harris, of Atlanta, who has given a large part of his professional life to the study of this disease, writes as follows:

“Without any practical acquaintance with pellagra worth speaking of, clearly ignoring the enormous amount of work that has been done on the etiology of this malady, Sambon some years ago halted long enough, in a flying trip across Italy, to inform an expectant world, even by telegraph, that he had discovered the cause of pellagra. Before leaving England, he in some way succeeded in having a ‘pellagra commission’ formed, though his writings do not make clear just how this was done. On this commission were some of the greatest names of contemporary medicine, and undoubtedly if any other of its members had taken part in the work the results would have been far different. As it was, Sambon appears to have proceeded alone to Italy, whence in a few days, as before stated, he announced the discovery of the cause of pellagra, and the method by which it is transmitted. It would appear that he left his own country obsessed with the idea that pellagra is an infectious disease transmitted from man to man by some biting insect, and with admirable quickness of decision he immediately inculcated a wholly suppositious parasite and assumed that it is transmitted by one of the small gnats of the genus *Simulium*—all of which are affirmed without a shadow of proof, and in direct contradiction of the general laws which we know usually govern the development and diffusion of those animal organisms that are transmitted by intermediate hosts.”

Babes, of Bucharest, writes as follows:

“An English commission, which had probably never before seen pellagra, on arriving in a region where the disease was common, and after seeing the pellagrins, and observing that there was a small gnat which produced a redness on the skin immediately after biting, promptly telegraphed to the world that the insect was the cause of pellagra.”

As to Sambon’s work as an epidemiologist, it must speak for itself, but, that he has some reputation among recognized authorities, is shown by the statement made by Castellani and Chalmers in the 1919 edition of their *Manual of Tropical Medicine*. These authors evidently think that there is important evidence in favor of Sambon’s contention. They claim that pellagra is most common in the vicinity of running streams and that probably it is transmitted by some insect breeding in such streams. They say:

“In general it may be stated that inquiries of this nature show that by far the larger number of cases occur in country districts, and not in towns, and that the densest localization is in houses near or alongside streams. In fact, study the localization in what country you will, as we have done in France, Spain, Italy, Austria, Hungary, Roumania, and Egypt, and it is impossible not to be impressed with the relationship between pellagra and water. Generally the water is moving, and often it is moving rapidly, but this last does not appear to be absolutely necessary. As a rule, the nearer the dwellings are to such water, the greater the number of cases. Cases do, however, occur at a distance from water, but inquiry will often demonstrate that the affected people work near or have been in some way connected with a stream. Cases do occur in towns, but they are relatively few, and careful inquiry will usually recall a perhaps almost forgotten fact that the disease really began

after some visit to the country. Inquiries, however, must be made with care, otherwise wrong impressions may be obtained. One of the most interesting cases which we have met with was that of a young boy who was supposed never to have left a large town, and yet was suffering from pellagra. Careful inquiry elicited the fact that he was in the habit of going for a day or so every year to stay with some relatives who lived in a pellagrous area, and the time of year chosen for this visit was one in which acute cases occurred. In a locality pellagra usually occurs among the poor, especially among field laborers; but it may also occur among the rich and among persons who habitually work indoors; it is, however, usually not difficult to trace a relationship between the commencement of the disease and a visit or residence in some pellagrous area, and very often, again, a relationship to water."

Castellani and Chalmers make the following further statement:

"With regard to the theory of a biting fly, Sambon is supported by the inquiry into the pellagra of the Island of Burano made by himself, Colonel Belli, and one of us, in which it was found that the fishermen and the boys who went fishing with them, were attacked by the disease, while the men who worked in the Venice Arsenal were said by the medical authorities to be free from the disease. The women, the girls, and the young children showed no signs of pellagra, with the exception of two or three women, who gave a history of working on the mainland or on other islands adjoining. Many of these young children, girls, and even women, were alleged never to have moved from Burano, with the exception in some instances of an occasional visit to Venice. These points are contrary to the maize theory, as all the inhabitants of Burano eat maize. They are also against an hereditary transmission of the disease, for with pellagrous fathers it would be imagined that the young children should show signs of pellagra, especially as the male influence is said to be preponderant by those who believe in the heredity of pellagra. They are against sexual infection, as the women would acquire the disease; they are against infection by contact, by kissing, etc., because certain men and boys have the disease, but the women and girls are remarkably free; they are against a parasite being carried from the sick to the healthy by house parasites, such as bugs or fleas, or personal parasites, such as lice. The difference between the persons who suffered from pellagra on Burano and those who did not, appeared to be the fact that the former either worked upon other islands or fished on the lagoon and up the streams leading into the lagoon. On the other islands and on terra-firma there are plenty of pellagrins, and everywhere there is a history of small black biting flies occurring on quiet days in the early morning or late evening."

Similar instances, which he interprets in favor of his theory, are given by Sambon in his progress report on the investigation of pellagra published in 1910. Undoubtedly, Sambon was premature in his announcement incriminating a gnat of the genus *Simulium* in the transmission of pellagra, and it seems to us that the weight of evidence, especially that furnished by the researches of Goldberger, is in favor of the theory that pellagra is not a transmissible disease but is due to an unbalanced dietary. This opinion, we do not, however, hold as final. The problem of the causation of this disease is still without decisive and unquestionable solution. It is possible that there may be two, and even more, factors concerned in the causation of the disease. While Goldberger and his assistants inoculated lower animals, including apes, and even them-

selves, with every secretion and excretion from pellagrins with negative results, the effects might have been different had the experimental animals and the men been previously prepared by long continued feeding upon an unbalanced diet.

In 1910, Long, having found amoebae in the stools of 50 persons out of 52 suffering from pellagra, suggested that the disease might result in consequence of injury to the intestinal mucosa by these parasites. That pellagrins frequently are infested with amoebae there can be no doubt, but this does not establish in any way a causal relationship between these parasites and the disease. Thousands of people carry amoebae in their intestines without developing pellagra; on the other hand, thousands of pellagrins never carry amoebae. Moreover, even the intestinal lesions are not the same in the two diseases.

The geographical distribution of pellagra coincides very closely with that of the use of maize as a human food. Moreover, as has been shown by the history, the discovery of pellagra in various parts of the world has followed the introduction of the use of maize as a food in the several countries. These facts are so striking that most of the theories concerning the causation of pellagra are based in one way or another upon the use of Indian corn. Maize theories have been put forth in a great variety of forms, some of which it shall be necessary for us to consider.

It was first suggested by Fanzago in 1807 that maize is the cause of pellagra, because this food is lacking in some constituent necessary for the proper maintenance of health. This theory does not presuppose the presence of any poison in the maize; it simply assumes the lack of some constituent essential to a well-balanced diet. It is a well-established fact that proteins are made up, or are polymers, of amino acids, and in order that the tissues of the body may be properly constructed, the proteins of the food must not only contain all the amino acids needed in the construction of muscle, nerve, etc., but must contain these amino acids in sufficient quantity. Now, the chief protein in maize is zein. It has been shown by animal experimentation that when zein is the only protein in the food, health and life cannot be maintained. At least two amino acids, tryptophan and lysin, are essential to the growth of young animals and to the maintenance of health in adults. Neither of these is found in zein. There must be something else lacking in zein, however, because when these amino acids are added to the food containing zein the mixed product does not support health and growth. It will be seen from these statements that maize, whether it causes pellagra or not, should not be the sole, nor, indeed, the chief protein in man's food. We are, however, compelled to state that up to the present time there has been no suc-

cessful attempt to induce anything like pellagra in animals by feeding upon maize. The effects of such food upon man will be discussed later.

In 1814 it was suggested by Guerreschi that maize, while in and of itself harmless, becomes poisonous on account of fungous growths or molds liable to form both in the unground and the ground grain, especially in the spring. This modification of the maize theory presupposes the formation of one or more poisons in the maize by the growth of molds. Much laboratory experimental work has been expended on this theory, the most noted exponent of which has been the great Italian criminologist, Lombroso. Italian pellagrologists, upholding this theory, point to the fact that pellagra is unevenly distributed in Italy, even among those communities subsisting largely upon maize. This is known as the "bad" maize theory. The original proponents of this theory point out the strong resemblance between pellagra and ergotism and urge the probability of the two resulting from related agencies. As is well known, ergot is a fungus growing on grain, especially on rye. All attempts, however, to test this theory by practical demonstration have failed. Moldy meal and decomposed corn meal mush have been extracted with all kinds of solvents and the extracts injected into man. One of America's most distinguished pellagrologists, Harris, of Atlanta, supports this theory in somewhat modified form. He states the reasons for his belief as follows:

"(1) It may be affirmed as a fact that pellagra existed in no country before the introduction of maize as a food. (2) That there are existing no records that show that this disease made its appearance in any place until this cereal had been used commonly as a food for approximately two or more generations. (3) That following the introduction of Indian corn into France pellagra became common in those provinces where it was usually eaten. About the middle of the last century, owing to the teaching of the French pellagrologists, maize was abandoned as a food for man, and pellagra gradually disappeared—the last case having been reported in 1902. (4) Pellagra has nowhere occurred in its endemic form except in those places where Indian corn is or has been consumed as food by man, and, with the possible exception of the tropics, this grain has been nowhere eaten where pellagra did not sooner or later appear. Even in the tropics the consumer of maize shows a high degree of degeneration. (5) If maize produces pellagra this result must be the consequence of intoxication. (6) We know that one of the constituents of maize is a tox-albumin—zein—and that it also contains poisonous ferments, and that it is possibly poor in the so-called vitamins; furthermore, in practically all instances where it is used as a food in spring or autumn it contains mold toxins (phenols). (7) In the amounts usually contained, these poisons produce little or no immediate effect, but it is wholly probable that their use throughout life, and from generation to generation, must be followed by evil consequences. (8) It is certain that chronic intoxications are highly hereditary. (9) It is known that in about 50 per cent of cases those who have pellagra are the offspring of parents, one or the other, or both of whom, have had the classic symptoms of this disease. (10) As pellagra frequently occurs without any of the classic symptoms, is it not possible that many, or even all, of the remain-

ing 50 per cent of its victims are the progeny of those who are afflicted with this mild form of the malady? According to the author's hypothesis this is assumed to be true, and therefore pellagra in practically all cases is thought to be hereditary. (11) This view is greatly strengthened by the fact that all practical pellagrolologists of the old world—where clinical data on this disease have been collected for nearly two centuries—unanimously hold that pellagra always lasts throughout life,—it being in truth the most chronic and intractable of all diseases.”

It will be seen from the above quotation, that Harris believes that pellagra results from an intoxication caused by poisons developed in maize by molds or other low forms of life; that such intoxications do not result in pellagra during the first generation, but that the disease develops in the second or third generation, especially when two or three generations have continued to eat maize; or in other words, to take the poison. As we understand it, Harris believes that pellagra may occur among people who have not eaten maize, provided this grain formed an important constituent of the diet of their ancestors. While it is true that certain chronic intoxications produce deleterious effects which are transmitted to offspring, it is rather difficult to believe that pellagra is, even in any considerable percentage of the cases, due to the physiologic sins of ancestors.

There is a smut (*urido maydis*) which grows upon corn, seldom abundantly, but more freely in certain years. It has been suggested that pellagra may be due to the mixture of this smut with food. Moreover, it is assumed that this smut is carried into the homes where the spores find their way into the meal chest, the mush, or any other of the many forms in which corn is served as a food. The reason that pellagra is more common among the poor is explained by supposing that their simple habitations become more thoroughly infested with these spores than do the homes of the well-to-do. There is no basis of experimentation for this theory and it may be dismissed as without support.

During the seventh decade of the last century, the distinguished Italian toxicologist, Selmi, awakened the attention of the world by his researches on the products of putrefaction. He believed that poisons are produced in corn and corn meal by bacterial growths. The theory of Selmi served a useful purpose in stimulating a study of the chemistry of putrefaction, but all attempts to isolate the pellagragenic poison have failed.

In 1915, Goldberger and Wheeler, of the U. S. Public Health Service, made an experiment, attempting to produce pellagra in healthy men. This experiment was carried out at the farm of the Mississippi State Penitentiary, a few miles east of Jackson. On an isolated spot in this farm of 3200 acres, there is a prison camp, with cottages for officials, a hospital, barn, stables, etc. During the period of the experiment there

were quartered at this camp an average of between 70 and 80 convicts, all white males. In this number were twelve, who, accepting an offer of pardon made them by Governor Brewer and with the assurance of proper care and treatment should such be needed, volunteered to submit themselves to the experiment. There had never been a case of pellagra on the farm.

The twelve men were quartered in what was called the "new hospital building," a small screened one-story cottage about 500 feet from the "cage" in which the other convicts were domiciled. From the time of its organization the squad was strictly segregated and under guard day and night. From February 4 to April 19, 1915, these men were kept under observation without any change in diet. Having detected no evidence of pellagra during this preliminary period and having established the desired routine of work and discipline, the diet was changed at noon April 19, 1915. On July 1, 1915, one of the men was discharged from the squad on account of prostatitis. This left eleven, with ages running from 24 to 50 years, who remained on the prescribed diet until October 31, 1915.

The quality and quantity of food consumed weekly by these men were as follows:

"Biscuits, 41.81 lbs.; corn bread, 24.56 lbs.; grits, 27.06 lbs.; rice, 24.25 lbs.; fried mush, 33.87 lbs.; brown gravy, 37.81 lbs.; sweet potatoes, 23.62 lbs.; cabbage, 4.25 lbs.; collards, 23.75 lbs.; cane syrup, 5.94 lbs.; making a total of 255.67 lbs. of food consumed during the week, or 3.32 lbs. per man per day, having a caloric value of 2,952 calories per man per day. The sugar was white granulated, the syrup home-made cane syrup. No vegetable fats entered into the diet. The corn meal grits were of the best quality obtainable in the local market."

The weekly work performed by these men was as follows: White-washing fences and buildings, two and one-half days; sawing lumber, two days, resting two and one-half days.

The entire population of the camp was kept under observation and served as controls. The work done by the volunteers was about the same as that done by the other convicts, such differences as existed were in favor of the volunteers, especially during the latter part of the experimental period. The general sanitary environment was the same for volunteers and controls, but the hygienic environment—personal cleanliness, cleanliness of quarters, freedom from insects, especially bedbugs—was decidedly in favor of the volunteers.

Of the eleven men on the above given diet not less than six developed symptoms, including a typical dermatitis, justifying a diagnosis of pellagra. The nervous and gastrointestinal symptoms were mild but distinct. The dermatitis was first noted between September 12 and 24, 1915, or not later than five months after the beginning of the restricted

diet. The skin lesion was first recognized in all cases on the scrotum. Later, lesions appeared on the backs of the hands in two cases and the back of the neck in one case. A diagnosis of pellagra in these cases was concurred in by Dr. E. H. Galloway, secretary of the Mississippi State Board of Health, Dr. Nolan Stewart, formerly superintendent of the Mississippi State Hospital for the Insane at Jackson, Dr. Marcus Haase, professor of dermatology in the University of Tennessee, and Dr. Martin F. Engman, professor of dermatology in the Washington University Medical School, St. Louis, Mo.

From these experiments, Goldberger and Wheeler concluded that pellagra had been caused, in at least six of the eleven volunteers, as the result of the restricted diet on which they subsisted. McCollum thinks that the dietary used in this experiment was deficient in three particulars: (1) Amino acids; (2) inorganic salts; and (3) fat-soluble vitamin A.

About the same time, Goldberger was given charge of two colored wards and one white ward in the large insane asylum at Milledgeville, Ga. For two years the occupants of these wards had, in addition to the asylum diet, meat and milk furnished by the U. S. Public Health Service. During this time all pellagrins in these wards were relieved of cutaneous and intestinal symptoms indicative of pellagra, but their insanity was in no way benefited. Moreover, pellagrins admitted to these wards lost the skin and intestinal symptoms within six months after being placed on the more liberal diet. There was no seasonal return of the disease or its manifestations among those afflicted and placed in these wards, while in other wards like improvements were not observed.

In addition to the above given experiments and observations, Goldberger had charge of a hospital for pellagrins at Spartanburg, S.C. In this institution the disease was studied and the only attempt to alleviate the symptoms was in the improved diet. Quite naturally, the conditions for the control of the patients were not so favorable as in the insane asylum at Milledgeville; however, Goldberger is convinced that his theory is supported in the results obtained at Spartanburg. It should be said that Goldberger does not claim that maize in the food is essential to produce pellagra. He thinks that the disease is due to an unbalanced diet in which proteins, especially animal proteins, are deficient. He points out that it is not only necessary that people should be provided with a balanced food, but that they should eat it. Taste for food, or for certain foods, seems to be a cultivated habit. It was currently reported in the army camps in 1917 and 1918 that those young men who had been subsisting for many years upon such an unbalanced diet as that given by Goldberger to his

volunteers, objected to a more varied food, and but slowly and reluctantly acquired the habit of enjoying a more generous ration. It has been observed in Italy and in other countries in which this disease has prevailed, that young men with the early symptoms of it enlisted in the army and placed on the army ration, lose the evidences of the disease, become quite normal, and suffer no seasonal recurrence. Apparently, this observation is in accord with the claim of Goldberger and his associates.

The cause of the skin lesions has received great attention and has awakened much discussion in all pellagrous countries, especially in Italy. These lesions so closely resemble those of sunburn that it is not strange that even the earliest Italian writers on this subject should have concluded that they are due to insolation. Gherardini wrote as follows on the subject many years ago:

"I was able to witness this action of the sun on certain pellagrins in our hospital, who had permission from their physician to go wherever they pleased. By means of small gifts and by persuasion I succeeded in getting a number of these patients to sit day after day for several hours with always the same part of the body exposed to the direct action of the June sun. After some days it was found, somewhat to my embarrassment and still more to theirs, that the parts had become red and shining, some being swollen and others not, the same being accompanied by a feeling of discomfort and a burning and itching; finally they became weak, the skin of their faces reddened, and they complained of vertigo."

Later, this matter was more scientifically studied by Bouchard, and especially by Raymond. The former covered a part of the arm of a pellagrous patient with a diachylon ointment, leaving a spot in the center bare. He found that only the unprotected area developed the erythema, and came to the conclusion that the skin lesions result from the sun's action. Raymond is of the opinion, which seems to be justified, that the sunlight plays a part in the production of pellagrademics, but is equally certain that it is not the sole cause. He concludes that the sun produces the effects as a consequence of the weakened condition of the tissues resulting from the pellagrous processes.

Harris writes as follows upon this point:

"It is likewise the experience of the author that pellagrademics frequently have their origin in exposure to the sun, it being an exceedingly common occurrence for intelligent patients to assert positively that their trouble began in this way—this particularly occurring in those who do not habitually labor in the fields, but who suddenly emerge from the confinement of the winter and engage in outdoor work. Even after a few hours' exposure, particularly in the spring, pellagrous patients often develop the erythema, and strange to say, this is almost invariably quickly followed by the other constitutional symptoms of the disease. It is likely, as the experiments of Gosio would seem to indicate, that toxins are produced in the body as a result of the skin lesions. It is also probable that the resistance of these patients is so lowered that the slightest disturbance is followed by the development of symptoms in other parts of the body."

It is quite certain that exposure to the sun's rays, especially in the spring, has some influence upon the development of the cutaneous lesions, but, that this is the primary cause, no pellagrologist claims. The skin of the pellagrin is a sensitive plate upon which sunlight has an effect, but the plate has been sensitized by some unknown agent, probably the poison specific to this disease. It is certain that, especially as far as the skin lesions are concerned, pellagra is a recurrent disease manifesting itself in these lesions most acutely in the spring.

Sunlight is not the only agent to which the awakening of the erythema may be due. It is likely to follow insults and slight injuries which do not have a like effect upon nonpellagrins. This point has received attention repeatedly from pellagrologists in Italy, Austria, France, and this country. Even the sting of a harmless mosquito, such as the culex, may be followed by a typical pellagrous dermatitis. Harris reports several instances in which slight blows on the hands have resulted in typical erythemas. Again, it seems necessary to suppose that this is due to altered innervation, lowered nutrition, or the presence of some poison in the blood. Harris makes the following statement:

"Just why the hands, feet, and face are the points of predilection in the development of these lesions is not entirely clear, but it may be pointed out that, with the exception of the volar aspects of the hands and feet, where the skin is remarkably tough and resistant, pellagrademics manifest themselves by preference on those surfaces that are most subject to insult, whether it be mechanical, or from such physical agencies as light, cold, and heat. Undoubtedly the most exposed parts of the body are the hands and here we find that the pellagrous lesion is most common, and after that and in the order named, the face, neck, feet, forearms, arms, shoulder-blades, and the skin about the middle portions of the chest in front where the shirt is often left open while the peasant is laboring in the field."

The skin lesion is not confined to erythema, but is accompanied by or followed by, or in rare cases, preceded by, a marked atrophy. The skin becomes thin, loses its elasticity, and presents a parchment-like aspect. When this stage is reached the lesion remains throughout life. According to Harris, it is a consequence of the absorption of the collagenous tissues, and the degeneration of the elastin of the derma, there being left of the normal structures the sebaceous and sweat glands, with the larger arteries and veins with enough fibrous tissue around them to give a certain amount of support. In such cases there may appear hemorrhagic spots; indeed, these are not uncommon in chronic forms of the disease. The hemorrhages are undoubtedly due to the rupture of small blood vessels, produced probably in most instances by injuries so slight that the patient is often not aware of their occurrence.

The cause of the alimentary symptoms which generally follow, but may precede the appearance of the skin lesions, is not known. The changes in the oral cavity are almost wholly confined to the superficial layers of the

mucous surfaces, and these are not uniformly altered. There may be marked exfoliation of the epithelial coating of the tongue. Not uncommonly, the lesions are localized along the borders and at the apex of the tongue. There is in some instances an abnormal flow of the saliva and difficulty in mastication. Fissures of the tongue are frequently observed.

There has been no uniformity in the findings obtained by analysis of the gastric contents. The acidity may be normal, subnormal, or above normal. Lactic acid may or may not be present.

In all pellagrous countries many pellagrins are found in the insane asylum. Numerous attempts have been made to associate certain forms of insanity with this disease, but up to the present time nothing definite can be stated in regard to this matter.

One of the most interesting points connected with this disease is its seasonal recurrence. It is a fact, popularly known for many centuries, that skin lesions are prone to development in the spring. The most reasonable explanation is that during the winter the small farmer lives under unhygienic conditions, has but little variety of food, and suffers from lack of exercise. The periodicity of symptoms originally induced by poisons is a matter about which much has been said, but concerning the reliability of which there is reason for doubt. It is a popular belief that children who have been poisoned by ivy have a recurrence of the skin eruption about the same season each year and without renewed exposure. We know of no authentic instance of this kind. Similar stories are told concerning the annual recurrence of symptoms after bites by certain reptiles.

McCarrison (1921) has been impressed by the parallelism in symptoms and anatomic changes produced in monkeys when fed on autoclaved food with those observed in pellagrins. He states that the similarity

"is evidenced by the loss of appetite, the headache, the wasting, the unhealthy skin, the malnutrition of the nervous system, and especially by the gastrointestinal derangements. The last are in both instances among the earliest manifestations of morbidity. Diarrhea, often with mucus and blood, is a conspicuous symptom in pellagra, as it is in the case of monkeys fed on autoclaved food. Gastric derangement is common to both. Failure of pancreatic and intestinal digestion, with the rapid passage of the gastrointestinal contents along the digestive tube, are features present in both states. * * * The parallelism extends to profound suprarenal inadequacy, the presence of which is suggested by the clinical features of pellagra. * * * Now, in the monkeys the main food fault was deficiency of vitamins. This deficiency gave rise to grave endocrin disturbance and especially to suprarenal disturbance. It caused the gastrointestinal lesions, and was primarily responsible for the imperfect assimilation of protein which occurred in these animals. It seems probable, therefore, that deficiency of vitamins and the consequent disturbance of digestive and endocrin functions play an important part in the production of pellagra. In the experimental diet employed by Goldberger for the production of pellagra in convicts, the food deficiency was of three orders at least: (1) Deficiency of suitable protein; (2) deficiency of growth vitamins; and (3) deficiency of salts. This diet has been shown by Sullivan to produce polyneuritis in fowls. It may be

concluded, therefore, that deficiency of vitamin B was an important factor in the production of the endocrin and digestive disturbances in convicts. Goldberger himself draws attention to the smaller average supply of recognized vitamins in the dietaries of pellagrous than of nonpellagrous households.”

Eradication.—Economically, the question whether maize is in and of itself poisonous or carries the possibility of leading to racial deterioration after it is used throughout successive generations, is of the greatest importance. Indian corn is one of our best crops. Prepared in any one of the many ways so well known to the cooks of the South, it supplies a most delectable article of diet. In our opinion, it would be a misfortune for the people of this country to be imbued with the idea that Indian corn is unfit for human food. So far as the weight of evidence goes, pellagra is due to an unbalanced diet. Geographically, it affects those populations which live most largely upon maize; however, sporadic cases are found in every part of the United States. Even the most radical zeists, as those who attribute the disease wholly to maize are called, admit that pellagra is found among those in the food of whom Indian corn has never played an important part.

As has been repeatedly shown, the workers in the cotton mills of our southern states have less variety in their food than any other laborers in this country. Many of them have never known any other diet than that upon which they have been reared and are reluctant to seek a more generous ration. It is difficult to awaken in man an effort to secure a food the taste of which he has never known. It is more than probable that pellagra can be completely eradicated from this country, provided that the people among whom the disease prevails are supplied with proper food and taught to eat it, and it will be interesting to see whether the army boys from pellagrous districts willingly go back to their corn pone and bacon. Man is not fitted physiologically to be a monophagist. He is an omnivorous animal; and whatever may be said by vegetarians, believers in low protein diet, and others who are constantly preaching that we eat too much, every fact learned by observation among people on limited diet, whether it be the result of war or of economic conditions, shows that man needs variety in his food.

We do not consider the question of the causation of pellagra by any means settled. It is said that in Spain the disease is slowly disappearing and that in the provinces where it was once common it is now rare, although no special efforts have been made to improve the food of the people. Its disappearance from France is attributed to the discontinuance of maize as a human food. In Italy, where the greatest efforts have been made to combat the disease by limiting the use of maize or by taking such steps as have been found necessary to prevent the molding of this food, up to the present time the decline in the disease has not been rapid, though there

has been a gradual improvement. There are the following species of corn grown in this country and more or less used as human food: (1) *Zea mais saccharata*, or sweet corn; this is used as an early vegetable and is canned. (2) *Zea mais indurata*, or flint corn; in this variety the starchy material is inclosed in a heavy horny layer. In color the grain may be white, yellow, red, or mottled. This variety is cultivated in the northern part of the United States and in Canada. Meal made from this variety does not mold quite so readily as that made from field corn; however, meal from either

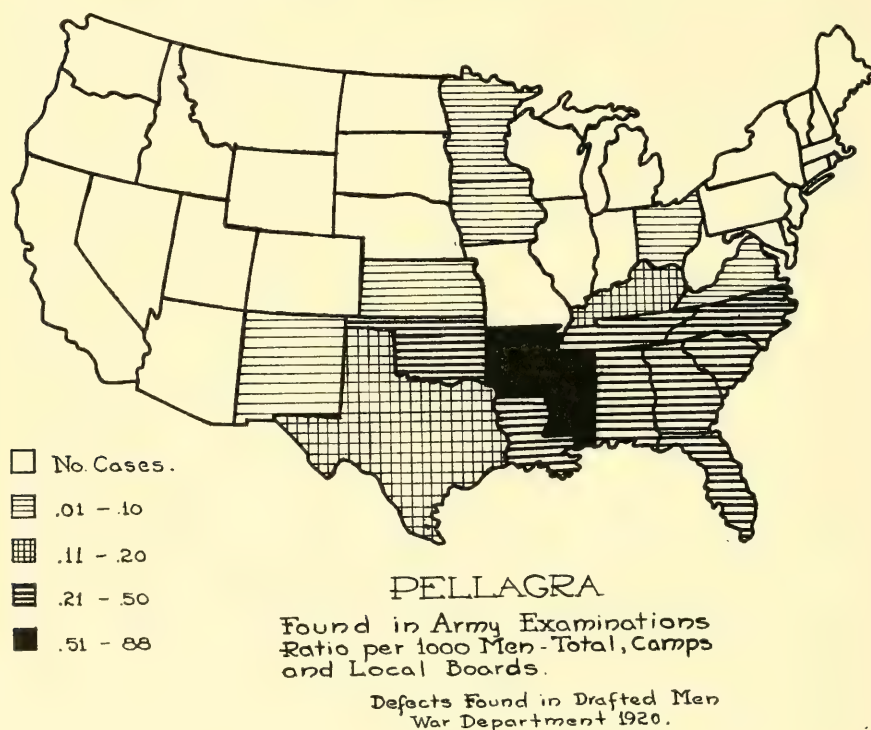


Fig. 1.

variety is highly subject to moldy growths and to decomposition, due possibly to other agencies. (3) *Zea mais indentata*, dent or field corn; this is the variety which is so largely eaten in the South, but which grows even more luxuriantly in Illinois, Iowa, Missouri, and adjoining states and supplies the great bulk of the corn crop. Whether moldy corn meal causes pellagra or not, it is certainly not a desirable article of diet, and it is gratifying to know that various state agricultural stations are giving attention to this matter and instructing the people in the proper selection of grain for planting, in the care necessary in harvesting and preserving, and in attention to the meal after grinding. To any one familiar with

the corn fields of this country, it must be evident that gross carelessness along all these lines among our farmers is still in evidence.

An indication of the distribution of pellagra in this country is obtained from the army examination. There were found 252 cases among two and a half million men. Of this number 236 came from the rural districts and only 16 from urban. The ratio of rural to urban incidence was 6.5, the highest ratio of any defect. Mississippi is credited with the highest incidence, or .88 per 1000 men. Other states in order were Arkansas .52, Florida .46, South Carolina .46, Tennessee .46, Alabama .42, Georgia .39, Oklahoma .31, Louisiana .27, North Carolina .25. States with rates from .10 to .20 were Texas, Kentucky and New Mexico. Rates of .01 to .09 were Rhode Island, Virginia, Iowa, Kansas, Minnesota and Ohio. No cases were found from the remaining states. Pellagra deaths in the U. S. Registration Area rank close to whooping cough in numbers. The death rates from 1911 are as follows:

1911	1.1	1916	3.3
1912	1.1	1917	4.9
1913	1.6	1918	4.6
1914	2.4	1919	3.3
1915	4.2		

The addition of southern states to the Registration Area in recent years explains the increase during the 10 year period. The ten states with the greatest numbers of pellagra deaths in 1919 were:

Mississippi	495	Virginia	177
Tennessee	435	Florida	125
South Carolina	401	Kentucky	111
North Carolina	400	Missouri	25
Louisiana	227	California	23

The fact that pellagra is so distinctly a rural disease is worthy of the closest consideration. Roberts has shown that occupation has nothing to do with it. Country, village merchants, lawyers, ministers, teachers, doctors, etc., have the disease quite as frequently as those who labor in the fields. Indeed, pellagra is more frequently found among women than among men. This seems to be true the world over. In a village in Italy, out of 254 pallagrins, 192 were women. In Roumania, out of 19,796, 10,664 were women. In an Illinois asylum, out of 130 cases, 75 were women.

In the U. S. Registration Area during 1919 there were 2806 deaths from pellagra, 2015 of which were among women and 791 men. The age distribution of these deaths by sex shows that at age 20-29 the female deaths are more than seven times that of males.

AGE	MALE	FEMALE	AGE	MALE	FEMALE
Under 5 years	21	19	30-39	76	442
5-9	25	17	40-49	142	416
10-14	13	30	50-59	133	270
15-19	19	79	60-69	169	212
20-29	49	371	70 and over	137	143

In our opinion, this greater prevalence among women makes in favor of the unbalanced and inadequate diet as the cause. When food is scanty, both in quality and in quantity, the man of the house and the children get the bigger helpings and the more choice dishes, while the mother takes what's left. This condition frequently prevails in families who would resent any suggestion that they did not have enough to eat or that any member of the family denied herself in order that others might more fully gratify their appetites. In the country pellagra is not confined to the poorest classes—of course it is more abundant among these people, but the better-to-do do not escape it. In the city even the poorest do not have pellagra. In the country the daily ration consists of only a few articles and is subject to but little variation from day to day. The wife or the children of the man who works in a cotton mill cannot get milk, cheese, or any great variety of food, for two reasons. First, because they have not the money to buy it, and, second, it is not to be found in their neighborhood had they the money. On the other hand, the poorest dweller in the east side of New York may step to the corner grocery at any time and buy a few cents worth of almost any kind of food, be it a staple article of diet, or a delicacy purchasable in large quantities only by the rich. This, in our opinion, is the explanation of why it is that pellagra is confined to rural communities and is not found within the gates of the city. It may be said, greatly to the credit of the owners of many of the cotton mills in the South, that they have tried to eliminate this disease and have spent, some of them, large sums of money in doing so. Some of the cotton mill villages are models in housing, in sanitation, in water-supply, and sewage disposal. By these improvements, typhoid fever has been greatly reduced and in many villages completely eliminated; but these expenditures have had, as yet at least, no visible effect upon the prevalence of pellagra. What the operatives and their families need is a greater variety of food. Some attention is now being given to matters of this kind. Operatives are encouraged to keep cows; land is donated for vegetable gardens, and people are encouraged to plant, till, and gather the fruits of these plots. We have had opportunity to visit many cotton mills in the South, to inspect the homes of the operatives, to study cases of pellagra among the adults and children, to talk with the owners, and we believe that the latter are only awaiting intelligent guidance. They appreciate

the fact that the pellagrin is unable to work and soon becomes a burden upon the community, the chief weight of which falls upon the mill owner.

Bibliography

- GOLDBERGER, J., AND WHEELER, G. A.: U. S. Public Health Reports, 1915, xxx, 3336.
HARRIS, H. F.: Pellagra, New York, 1919, The Macmillan Company.
MARIE, A.: Pellagra, Translated by Lavinder, C. H., and Babcock, J. W., The State Company, Publishers, Columbia, S. C., 1910.
ROBERTS, S. R.: Pellagra, St. Louis, 1914, C. V. Mosby Company.
WOOD, E. J.: A Treatise on Pellagra, New York, 1912 D. Appleton & Company.

CHAPTER VI

RACHITIS

RICKETS

Description.—Rickets is a constitutional disease, characterized by abnormal development of the processes of osteogenesis and manifesting itself most prominently by deformities of the bones. The proportion of organic and inorganic constituents of the bones compared with that of the normal state is practically reversed. Normally about 65 per cent of the bone is inorganic material, while in rickets the percentage of organic substance may be as great as this. On account of the relatively small amount of inorganic matter in the bones in this disease, these structures become soft and pliable and marked deformities result, some of which are easily recognized at sight. While all the bones in the body may show this abnormality, deformities are most markedly developed in the long bones, especially in those of the lower extremities, leading to the conditions vulgarly known as bow-legs, knock-knees, and rickety states. The chief inorganic constituent of bone is the phosphate of lime and it is due to failure in the normal metabolism of this essential food constituent which leads to the disease. The long bones are so soft and pliable that they may be bent by muscular action long before the weight of the child is put upon them in its first attempts to walk. The epiphyses in the ankle, knee, and wrist are enlarged, while the shafts of bone may be bent and twisted. There are swellings on the ribs where they join the sternum, forming what is known as the rachitic rosary. The ribs are often sunken and the sternum thrown forward, giving rise to what is known as the pigeon or chicken breast. The bones of the pelvis are often twisted into abnormal shapes and the vertebral column may be deviated either posteriorly or laterally, kyphosis, and less frequently a scoliosis. Chemical analysis has shown that the amount of lime may be reduced to about one-third the normal quantity. There may be a depression of the diaphragm, dilatation of the stomach, together with hypertrophy of the liver and spleen. These conditions lead to an undue proportion of the abdomen, a condition vulgarly known as pot-bellied. The whole being is in a state of disordered metabolism, from which there is in the majority of instances a tardy recovery with persistence of the deformities.

History.—Strange to say, this disease was first recognized in the early half of the seventeenth century as an epidemic appearing in Dorset and Somerset in England and gradually extending throughout that country.

It is difficult to believe that this disease first appeared at that time. It must be as old as the race, and it is rather strange that it was not recognized and studied earlier. The Royal College of Physicians appointed a committee to investigate this disorder. A report was written by Glisson and published in 1650. Comby says:

“This is the earliest known publication on the subjects of rickets, and the history of the disease does not go back beyond this time; but when we consider the dyscrasic origin of the affection, which is a true *maladie de misère*, we are forced to refer its origin to a more remote period.”

In continental Europe this disease was for a long time known as the English disease. In 1660 Mayow wrote upon rickets and called especial attention to the changes in the bones. In 1741 Petit advanced the idea that it is due to premature weaning; an idea which no longer has support. In 1751 Duverney studied the bones more minutely, emphasized their lightness, fragility, and proneness to suffer a green-stick fracture. In 1797 Portal, including many other diseases along with rickets, divided it into seven varieties. Guérin (1839) added to the knowledge of the histology of the disease and was, so far as we know, the first to attempt to produce it by experiments in the feeding of animals. Trousseau and his colleagues made important contributions to the pathology and symptomatology of rickets and called attention to its relation to osteomalacia. Parrot (1881) conceived the idea that rickets is a form of hereditary syphilis. Jacobi says, that Parrot was led to this conclusion by the deformities and abnormalities in the teeth. During recent years the literature on this disease has become voluminous, and the more important contributions will be referred to in the study of its etiology and its nature.

Etiology.—Most writers of the early part of the nineteenth century taught that rickets is an hereditary disease, or, at least owes its existence to a defective constitution in one or both parents. Some attribute it to early marriage, some to close inter-marriage, and most authors are convinced that the existence of the disease is due to some parental defect. Aitken (1879) taught that, while the disease is not inherited, its predisposing causes lie in the bodies of the parents, which have been exhausted by age, chronic disease, and venereal excesses. The suggestion of Parrot that rickets is inherited syphilis was again taken up, but it was so earnestly and intelligently combated that it did not thrive. In 1860 Jenner (W.) wrote:

“The parent who infects his offspring with syphilis has usually contracted syphilis before marriage, and the children first begotten after infection are those who suffer from inherited syphilis; while, as a rule, it is only the younger children of the family that suffer from rickets—the first-born being commonly healthy, though the latter-born are highly rickety.”

Jenner attributed the disease, largely at least, to undernourishment or improper food and wrote as follows:

“Among the poor, the parents are generally worse fed, worse clothed, and worse lodged, the larger the number of their children—for the man’s wages remaining stationary, the calls on his means are increased. And among the rich and poor alike, the larger the number of children, the more has the mother’s constitutional strength been taxed, and the more likely is she to have lost in general power.”

The same author speaks of the feeding of the poor children of his time in London, as follows:

“For the first two or three days after birth their tender stomachs are deranged by brown sugar and butter, castor oil and dill water, gruel and starch water; as soon as the mother’s milk flows, they are, when awake, kept constantly at the breast. And well for them if they are not again and again castor oiled and dill watered, and even treated with mercurials—for the poor have learned the omnipotent virtues of gray powder.”

Jenner, writing in 1860, said that rickets is in England the most fatal disease which affects children exclusively. At that time rickets was not so common in our American cities, or at least it was not so recognized. In the nine years ending with 1870 the mortality records of Philadelphia reported but two deaths from this disease. Comby (1896) wrote:

“If the mother is able to nurse her infant and give to it all the care which its age demands it will not become rachitic; but separate these two beings who are made to be closely united, give the child to mercenaries living at a distance and secure from surveillance, replace the breast by the bottle, and you will almost surely provoke rickets. Where the bottle is unknown, where infant feeding is always from the breast, there rachitis is absent. It is frequent under the opposite conditions. Next after artificial feeding comes suckling by a poor nurse, one whose milk is too old, indigestible, or which contains too large a proportion of casein; then irregular times of nursing, and finally a delay in weaning and in the admission of solid food to the infant’s diet at a suitable period. When a woman nurses twins she can very rarely do so with justice to both children, and the infants are apt to suffer from rachitis.”

Jacobi (1898) wrote:

“Hygiene and nutrition are of great influence. There is less rachitis in rich or well-to-do families than among the poor. There are very many exceptions to this rule from different causes. Bad foods, such as large percentages of amylum or undiluted cow’s milk, are dangerous; but when babies are fed on the same faulty diet in the valleys and on the high Alps, those on the latter suffer less from rachitis; it is particularly undiluted milk that is better tolerated on the high mountains than in the valleys. In the favorable climate and outdoor life of Athens, where the babies are mostly weaned after the second month and farinacea given, rachitis, as I said, is not frequent. Breast children suffer less from rachitis than those raised on artificial food, still, there are plenty of babies whose breast milk contains an undue degree of casein that require weaning, and will require a well-selected artificial food in order to get well of their rachitis.”

In 1895 Herter fed pigs upon a fatless diet with the purpose of determining whether such food would produce rickets in these animals. He took pigs about two months old and weighing about 24 pounds and placed them upon an exclusive diet of cow's milk from which the fat had been removed to such an extent that the milk contained less than one-twentieth per cent of this constituent. It should be stated that sow's milk normally contains a high percentage of fat, ranging from eight to ten per cent. Herter found that the growing pig, living exclusively upon this fatless milk for about a year, suffered markedly by retarded growth and developed a hemorrhagic eruption, which was probably scorbutic in character, and was accompanied by marked weakness in the extremities. A second pig kept on the same diet for 66 weeks developed similar conditions, but in a less marked degree and without the hemorrhagic spots. A third pig kept upon a diet greatly restricted in proteins and fats but with a great excess of carbohydrates, although more retarded in growth, suffered distinctly less in general nutrition and apparently in a different manner in several respects. Herter reached the conclusion that the lesions resulting from fat starvation, at least in the case of pigs, do not resemble, or even suggest, those of rickets.

Herter's conclusions are not altogether in harmony with those reached by Sutton, who fed young monkeys, bears, and lions in the Zoological Garden of London on diets rich in proteins but deficient in fat. The animals thus fed are reported to have developed rickets, while those to whose diet fat was added, remained free from this disease. Furthermore, Herter's conclusions are not in accord with the beneficial results quite generally obtained by treating rachitic children with cod-liver oil.

It having been suggested that atrophy of the thymus gland might be concerned in the causation of rickets, Renton and Robertson removed this gland from a number of puppies. These animals were subsequently kept on the same diet, which consisted of oatmeal with milk, and bones to gnaw. Some developed rickets, while others did not; the immunity of the latter seeming to depend upon the breed rather than from the mode of life. Of the collies, all developed rickets; of the retrievers, two developed the disease and one remained normal; of two fox terriers, both showed slight signs of rickets, while two greyhounds remained normal.

Hess and Unger state that negro children in New York City are much more prone to this disease than white children, although both are fed upon the same diet, receiving milk from the same dealers. This is a further indication that race or breed has some influence on the development of rickets.

Paton is quite certain that confinement is concerned in the development of this disease in dogs. Two litters of collie pups were divided, one part being sent to the country where they were allowed the run of

yard and garden, while the other was kept in the laboratory. Both lots were fed upon practically the same diet. No animal sent to the country developed the disease, while all those kept in the laboratory showed signs of rickets to a greater or less degree.

Hess and Unger undertook the study of rickets in about 100 children cared for in a modern institution in New York. These children were divided into groups according to their food: (1) having an abundance of fat and fat-soluble vitamin in the form of milk and cream; (2) with a deficiency of these substances, being fed on skimmed milk; (3) with an abundance of water-soluble vitamin as supplied in autolyzed yeast; (4) on a diet such as Mellin's Food or condensed milk. All of these children were examined monthly, special attention being paid to the development of the beaded rosary on the ribs, with the full recognition that this condition may be scorbutic and beriberic as well as rachitic. These authors state their conclusions as follows:

"It would lead too far afield to discuss the various theories that have been advanced to account for the occurrence of rickets, and moreover, it would not be profitable at the present time, as the data are inadequate. There seem to be several causes at work, rendering the unraveling of the problem so difficult that there is a difference of opinion not only as to the particular dietary factor that is at fault, but even as to whether rickets is to be considered a disorder of dietetic origin. It should not be lost sight of that there is a prenatal factor involved. * * * In considering the diet a most important question is whether the recent theory as to the vitamin origin of this disorder can be maintained, and, more particularly, whether rickets should be attributed to a lack of the fat-soluble factor. We can obtain the clearest understanding of this aspect by comparing this disease to the well-recognized and established deficiency diseases, scurvy and beriberi. What does the comparison show? In the first place, these two disorders are commonly accompanied by weakness and malnutrition; we do not encounter the strong, apparently healthy babies met in rickets. But of far greater moment is the fact that neither can be brought about by overfeeding. Rickets, as emphasized in the body of this paper, frequently develops in infants receiving too much milk rich in fat, protein, and salts. It seems impossible to bring this fact into consonance with a deficiency disease, whatever may be its nature, using this term in the commonly accepted sense. Our study shows that the fat-soluble vitamin is not the controlling influence; that infants develop rickets while receiving a full amount of this principle, and that they do not manifest signs, although deprived of this vitamin for many months, at the most vulnerable period of their life. It is impossible to interpret the contrary conclusion which Mellanby came to as the result of his pioneer experiments on dogs, or to accept the term 'fat-soluble vitamin' as synonymous with 'antirachitic factor,' as Hopkins and Chick would have us do. Clinical tests carried out with care must be accorded fully as much weight as laboratory investigations. The two methods of approach should be carried out side by side, and even the most thorough study on animals must be made to harmonize before it can be accepted as holding good for man."

Neff, writing in 1920, says:

"Funk's hypothesis of the *absence* of an essential food factor, which he considers a

vitamin, has caused rickets to be regarded by some as belonging to the so-called deficiency diseases. But the best explanation thus far given is that rickets is the *result of too much food*—usually artificial—exceeding the caloric requirements of the individual child and its ability to dispose of it. The one fact known is that with the appearance of rickets there is deficient calcium retention in the bones and increased loss of the mineral by way of the feces and urine. The amount excreted in this way may exceed the intake even on an adequate diet.”

Mellanby is at present the most active supporter of the theory that rickets is due to the absence of a vitamin in the food. He thinks this substance is a fat-soluble vitamin, although it differs from that described by McCollum, inasmuch as the antirachitic vitamin is found, according to Mellanby, in certain vegetable, as well as in animal, fats. His conclusions may be summed up as follows: Confinement, so far as the diet is concerned, will not produce rickets and will not prevent the cure of this disease, so far at least as the growing ends of the bones are concerned. Furthermore, exercise, with a free run in the daytime, will not prevent this disease when the diet is inadequate. This author seeks confirmation of this experimental work on dogs. In a report made by Hall some years ago concerning the comparative prevalence of this disease in Jewish and Gentile children at Leeds, he found rickets, together with bad or backward teeth, much more prevalent among Gentile than among Jewish children. This holds good whether the comparison is made between the rich or the poor. The greater freedom of the Jews from this disease is ascribed by Hall to the better dietary at home of Jewish children, and especially to the larger amount of fats consumed in these families.

Mellanby finds further confirmation of his ideas from a study of the physical condition of children on the Island of Lewis in the Hebrides. These people, he states, live in stone houses, thatched with straw, the living-room often being under the same roof as the cow house and with chickens running about in all parts of the stable and house, roosting on beds, tables, and dressers. These stone houses, the walls of which are often five feet thick, have no chimneys and the constantly burning peat fire keeps the room filled with smoke, the only egress for which is the door. Children under one year of age are never taken out of the house and the infantile mortality is said to be about the lowest in the British Isles. The food consists of fish, oatmeal, and eggs, with milk scarce except in summer. While the death rate under one year of age is low, that from one to five years is high. Mellanby says:

“It is difficult to avoid the conclusion that diet is everything to infants under one year, and, so long as this is good, bad hygienic conditions are of small significance. After the first year, however, when the child becomes susceptible to measles, bronchopneumonia, and other infections, then clearly the housing and hygienic factors in addition to the diet are of great importance. If these suggestions could

be definitely proved and accepted, we should have gone a long way towards the solution of the problem of race decadence. It is reasonable to accept as facts that where there is low infant mortality, there is an almost complete absence of rickets and the teeth of the people are good; also that the production of rickets depends on a *relative* insufficiency in the diet of the antirachitic accessory factor, the best sources of which are fish oils, animal fats, except lard, milk, eggs and some of the vegetable fats. It is also probable that anything which stimulates metabolism, such as high protein in the diet and exercise, aids the antirachitic accessory factor; while excess of carbohydrate, especially if it leads to a laying on of fat or a production of lethargy, works in a way antagonistic to the vitamin and makes it necessary to have a greater amount in the diet to insure normal growth of bone, formation of sound teeth and jaws, and good general health."

In a later (1921) report Mellanby says that the following conditions tend to prevent rickets in puppies: (1) Plenty of meat, fat, calcium and phosphorus in the food; (2) Exercise.

Glisson, in his original paper on rickets, came to the conclusion that a foggy climate favors the production of this disease in children. Palm, in 1890, after a study of the geographical distribution and etiology of this disease, stated his conclusions as follows:

"(1) The establishment of means for having systematic and exact records of the sunshine in the heart of our great cities as well as at favorite health resorts. A sunshine recorder at an observatory on some hilltop near a large city is no guide to the amount of sunshine that reaches the streets and alleys of smoky cities. It is important that the sunshine recorder be of the form which indicates the chemical activity of the sun's rays rather than its heat. (2) The removal of rachitic children as early as possible from large towns to a locality where sunshine abounds and the air is dry and bracing. (3) The establishment of a sanatorium for poor rickety children in some such locality, where the severe development of the disease may be averted, and much life and health saved by timely treatment. (4) The systematic use of sun-baths as a preventive and therapeutic measure in rickets and other diseases. (5) That when a mother has once borne a child which has become rachitic, preventive treatment of the disease in her future children should be adopted if possible by change of climate and mode of life in the mother, nothing urged above being inconsistent with the belief that the mother's state of health brought about by the same causes predisposes her offspring to rickets. (6) The education of the public to the appreciation of sunshine as a means of health. Many persons seem to prefer darkness to light in their dwellings out of ignorance, thoughtlessness, or even an economic regard for carpets and curtains. Let people understand that sunlight in the dwelling not only reveals unsuspected dirt, but is Nature's universal disinfectant, as well as a stimulant and tonic. Such knowledge will also stimulate efforts for the abatement of smoke, and for the multiplication of open spaces, especially as playgrounds for the children of the poor."

More recently, the value of sunshine both in the prevention and in the treatment of rickets has been substantiated by the researches of Powers and his coworkers, of Hess, and many others. This does not mean that the kind of food furnished the child should not be considered. It simply demonstrates that sunlight is essential to healthy metabolism.

A review of the literature reveals that two main factors are referred to as primal causes of rickets—confinement and improper diet. Authors differ widely as to the relative importance of the two. Quite recently, there has been offered evidence which would tend to harmonize the divergent views on this subject. We refer to the collaboration of Powers, Park, Shipley, McCollum and Simonds. They point out that confinement is a factor in rickets owing to the absence of needed sunlight stimulation on cell activity. They quote extensively from German and English works as showing the value of sunlight and even the ultraviolet ray from a quartz lamp in alleviating rickets. They experimented with 18 rats about six weeks old, to which they fed a rachitic-producing diet rich in calcium but deficient in phosphorus and fat-soluble A. Twelve of these animals were then exposed to sunlight, being left out of doors for six or more hours daily over a period of 62 days. The other six rats as controls were kept indoors in the laboratory in a room well ventilated and receiving all light through windows of ordinary glass. At the end of the period the control rats showed all the gross and microscopic evidences of rickets,

“the characteristic deformities of the thorax, enlargement and distortion of the costochondral junctions, fractures of the shafts, and enlargements at the wrists, ankles and knees, and the ends of all the long bones.”

The rats exposed to sunlight, however, showed no evidence of rickets. The ends of the long bones were not enlarged and cartilage was normal. The condition was normal except that the bone was more delicate than in rats of corresponding age fed on satisfactory diets.

“Though the sunlight completely prevented the development of rickets, it did not entirely compensate for the deficiency of phosphorus in the diet, as regards the growth and development of the rat as a whole or of the skeleton.”

The sunlight rats had plenty of fat, the controls little. It is significant that sunlight affected not the skeleton alone but every cell in the organism. The importance of this experiment is summed up in the following statement, which we quote at length:

“The exposure to the sun’s rays, however, did not entirely compensate for the defects in the diet. The animals remained undersized; the bones, though completely calcified, remained thin. Though the sunlight did not alter the defects in the diet, it permitted the animals to thrive to a limited extent in the presence of them.”

The authors conclude that the

“effects of sunlight and of cod-liver oil on the growth and calcification of the skeleton and on the animal as a whole seem to be similar, if not identical.”

We believe that this is the most important contribution to our knowledge of the causation of rachitis. It, likewise, has a far-reaching influence on our views concerning hygienic living conditions. It adds one more

bit of evidence to the value of the open-air and open-window treatment of anemic and tuberculous children. Sunlight is something that human nature demands, as well as the proper chemical balance in the food intake.

Conclusions.—After reviewing, as we have done, the most important clinical and experimental contributions to this subject, we must decline to accept the evidences offered in favor of the claim that rickets should be classed with scurvy and beriberi as a disease due to the absence of some unknown food accessory.

We think it safe to make the following statements concerning measures which should be adopted to prevent the development of rickets: (1) The diet of the pregnant woman should be carefully balanced, should be deficient in neither food principle nor vitamin, and she should have leisure and opportunity for outdoor exercise during gestation. (2) The infant should be breast-fed except when this is positively contraindicated, but the breast feeding should not be unduly prolonged and except on the advice of the physician it should not be continued beyond eight months. (3) After weaning, the diet of the infant should be carefully supervised and an excess of carbohydrate and a deficiency of fat should be avoided. No proprietary foods should be permitted unless specially prescribed by the family physician. (4) The child should be kept in the open air with free exposure of the greatest possible extent of its body to the direct action of sunlight for at least three hours a day in order to facilitate the digestion and absorption of food. (5) The use of the daily bath, followed by proper massage and passive exercise will serve as a tonic and aid proper absorption and assimilation.

Bibliography

- AITKEN, W.: Article on Rickets in Reynold's System of Medicine, i, 472.
 COMBY, J.: Article on Rachitis in Twentieth Century Practice of Medicine, vii, 529.
 HEETER, C. A.: Jour. Exper. Med., 1898, iii, 293.
 HESS, A. F., AND UNGER, L. J.: Jour. Am. Med. Assn., 1917, lxix, 1535; *ibid*, 1920, lxxiv, 217; *ibid*, 1921, lxxvii, 39.
 JACOBI, A.: Article on Rickets in American System of Practical Medicine, iv, 917.
 MELLANBY, E.: Proc. Roy. Soc. of Med., 1920, xiii, 57; Experimental Rickets, 1921.
 NEFF, F. C.: Tice's Practice of Medicine, ix, 145.
 PALM, T. A.: The Practitioner, 1890, 271.
 PATON, D. N.: Proc. Roy. Soc. of Med., 1920, xiii, 77.
 POWERS, G. F., et al: Jour. Am. Med. Assn., 1922, lxxviii, 159.
 RENTON, M., AND ROBERTSON, M.: Jour. Path. and Bacteriol., 1916, xxi, 1.

CHAPTER VII

ENDEMIC GOITRE AND CRETINISM

Introduction.—Modern research, beginning with the surgical procedures of Horsley in the implantation of the thyroid and with the therapeutic demonstration of Murray of the value of thyroid feeding, has furnished the material for many volumes, the pages of which are quite as interesting as, and far more informing than, the stories of the Arabian Nights. The thyroid gland has been compared to the governor which regulates the activities of the steam engine and to the carburetor which determines the efficiency of the automobile. For centuries, the anatomy, physiology, and pathology of this gland were wholly neglected and man was unaware of its great importance in the various functions of life. It has been found that the thyroid and its adnexa regulate the growth of cells and determine their activity. At present it seems that there is scarcely a life function in which this organ does not play an important part. Through its hormones it reaches every structure of the animal body and determines the rate of growth of cells, the wear and tear in their structure, and the elimination of their waste products. Apparently, it defends the animal body against the invasion of harmful microorganisms and the injurious effects of their products, whether they be in the form of secretions or result from a disintegration of the invading cells. McCarrison says:

“So far as we know its metabolic activities are exhibited in the following way. It regulates the oxygen intake and the carbon dioxide output. It maintains the constituents of the blood—the red cells, the white cells, the hemoglobin and salts—at a proper level. It has an important influence in regulating the body temperature. It controls the metabolism of those metallic ions necessary for cellular activity, and of albumins, carbohydrates, and salts; it influences the arterial tone and is thus concerned in the regulation of the blood pressure; it maintains the activity of the central and sympathetic nervous system; it controls excretion by its physiological diuretic action on the renal epithelium and by its action on the liver cells and excretory organs of the body; it stimulates in a specific way certain other hormone-producing organs, thus securing and controlling their cooperation in regulating metabolic processes; in short it maintains the efficiency of all cells and thus speeds up and keeps at a healthy level every biological function. The thyroid gland is to the human body what the draught is to the fire; nay more, its iodine, by its chemical interaction with certain unknown constituents of the cells, is the match which kindles it.”

Much has been written about the nerve supply of the thyroid gland and its nerve connections with other endocrine glands. All of this is of value, but, since it has been demonstrated that a thyroid implanted in

the abdomen, functions, we must conclude that communication between this and other glands is carried on largely by messenger rather than by wire.

Carrel reports that brain and other tissues cultivated *in vitro* grow much better in the presence of thyroid substance than when this is not a constituent of the medium. Gudernatsch has shown that feeding tadpoles on thyroid gland stimulates growth and hastens differentiation in the development of the vertebrate organism. When fed upon this gland, tadpoles reach the point of metamorphosis within 18 days after hatching, while normally it requires from 10 to 12 weeks to reach this stage. It should be understood that the accelerated growth secured in this way is not of the best quality. Marine and Rogoff have employed the method of feeding tadpoles with thyroid in the biologic determination of the efficiency of thyroid preparations and the effect of the administration of iodine on the hormone content of the gland.

McCarrison gives the following definition of endemic goitre:

“A chronic infectious disease occurring in more or less circumscribed areas and characterized by a noninflammatory and progressive enlargement of the thyroid gland, which is unattended by marked functional disturbances. It is due to the presence in the alimentary tract of certain undetermined organisms, whose toxic products reach the blood stream and induce in the thyroid gland hypertrophic, hyperplastic, and degenerative changes. Acting through the medium of the maternal blood, these toxins may cause hypertrophy and hyperplasia, or fibrosis and atrophy of the fetal thyroid, thus giving rise to congenital goitre or to the varying degrees of cretinism.”

It should be noted that when speaking of toxins this author includes all bacterial poisons.

History.—There is no certainty that the earlier Greek physicians knew anything about endemic goitre, although some of their statements concerning tumors of the neck have been so interpreted; on the contrary, Latin writers, Pliny, Vitruvius, Juvenal, and Ulpian, were aware of the fact that endemic goitre was at the time they lived frequently seen in certain Alpine localities. During the middle ages this disease is occasionally referred to, was regarded as a special punishment from God, and the legend that it could be cured by the touch of the King's hand, arose. In the stories of Marco Polo, this great traveler and wonderful narrator tells of its prevalence in certain regions of central Asia near the close of the thirteenth century. In his book, *De Generatione Stultorum* (1516) Paracelsus gives an account of his personal observations on goitre and cretinism and their relation among the inhabitants of Salzburg and the surrounding country. During the seventeenth and eighteenth centuries there appeared many books and pamphlets detailing observations made by physicians of those times in certain localities, mostly Alpine, where endemic goitre and cretinism prevailed. In 1789 there

appeared a book, entitled, "*Sui gozzi e sulla stupidita*" by Malacarne, giving the results of the observations and studies of this physician on endemic goitre and cretinism in the Valley of Aosta. This may be said to be the beginning of scientific records concerning this disease, and the Valley of Aosta has continued up to very recent times to be the favorite visiting place of those interested in diseases of the thyroid. Within the past 30 years, however, goitre and cretinism have practically disappeared from this region.

To those who are interested in the geographical distribution of endemic goitre and cretinism in the past, we recommend the very complete records of Hirsch, the last edition of whose work on this subject was published in 1885. Goitre has disappeared from so many of the places where it was then prevalent, and has been since recognized in so many places where it was at that time unknown, that it would be hardly profitable to abstract, even what Hirsch did, in minute detail. At present, goitre areas, some exceedingly limited, others very extensive, are found in all parts of subtropical and temperate zones. It should not be inferred from this that tropical and Arctic regions are altogether free from goitre. There are nests in tropical South America, Central America, the West and East Indies, and the disease is not unknown in Siberia, Finland, and far north in Canada. While endemic goitre is more prevalent at high altitudes, it is by no means unknown in low-lying valleys and on alluvial plains. All highlands do not harbor this disease, it being unknown in the mountains of Scandinavia and in the highlands of Scotland. In Europe and the United States there are certain localized areas in which enlargement of the thyroid gland is unusually prevalent. Within recent years some of the best studies have come from observations and experiments made in Himalayan villages, in some of which the disease is so common that it is difficult to find man, woman, or child not exhibiting this deformity. In most Alpine places where the disease was common forty years ago, improved sanitation has greatly reduced its prevalence.

In wild animals goitre is rare, but there is scarcely a species brought into domestication which is not susceptible and which does not develop the disease in the natural way. This is true of herbivorous and omnivorous animals, of mammals, birds, and fish. Certain domestic animals, hogs, sheep, horses, cattle, goats, and possibly others, suffer so severely from goitrous conditions that this at times constitutes a heavy economic loss. Among fish, trout and pike seem to be especially susceptible, while carp and salmon are less so. It is altogether likely, however, that the great frequency of goitre among trout is due to the frequency and abundance with which they are artificially bred and reared.

While there is no difference between endemic and epidemic goitre, the

latter term is used to designate the acute or subacute appearance of this condition in numbers of men passing from a nonendemic into an endemic area. This, of course, may happen to an individual or to a small party, but it has been observed that when troops are moved from a nonendemic into an endemic area considerable numbers are likely to develop goitre within a few weeks and the longer the continuance of residence of susceptibles in the endemic area the larger is the proportion of those affected. The first so-called epidemic of goitre was reported among French troops from 1783 to 1789. A regiment which had been garrisoned at Caen for five years was transferred to Nancy where the disease was slightly endemic in 1783. During the winter of 1783-1784, 38 of these men became goitrous; in 1785 this number increased by 205; in 1786, by 425. After the last given year the number gradually decreased, but during the six years 1,100 men out of four battalions developed goitre. There were a few cases in another military organization which had been stationed at Nancy for many years and a few cases among the civil population, but there was nothing like an epidemic except among the troops that had come from Caen, a nonendemic place. It was noted that the development of goitre was confined to the common soldiers and did not affect either noncommissioned or commissioned officers. One explanation given at the time for this discrimination was that the officers drank wine, while the men were compelled to be content with water. This interpretation seems to have been founded upon a presumption, and there is no probability that either common soldier or officer at that time in the French Army drank water. A more satisfactory explanation was that the immunity shown by the officers was due to the fact that they were housed more satisfactorily and were not brought into intimate personal contact. From that time quite to the present, similar epidemics of goitre have been reported in France, most frequently among young soldiers recently recruited from nonendemic areas and brought into crowded barracks in endemic places. These outbreaks in France have not been confined to soldiers. One was reported in a boarding-house in a village near Paris; another in a college in Strasbourg, and from a high school in Belfort. Several epidemics, both among troops and students have been reported at various places in southeastern France, especially along the Swiss border. In 1820 a battalion of recruits was assembled at Silberberg in Silesia. There were 380 of these and they were young men drawn largely, if not altogether, from localities in which goitre was practically unknown. Within a few weeks 70 of these presented markedly enlarged thyroids. In the Russian campaign against Turkestan in 1877 in one garrison of 2,753 troops there developed within a short time 245 cases of goitre. The troops were then removed to a nearby but nonendemic

area, and apparently there was no further progress of this abnormal condition. In a war between Brazil and Paraguay it is reported that when the Brazilian troops reached an area of endemic goitre they were so generally affected that *en masse* they deserted and fled to their homes. Numerous slight epidemics of goitre have been reported from boarding schools in France, Switzerland, Austria, and India. Various explanations have been offered. In most instances each such explanation satisfies so far as local conditions are concerned, but in all instances there is failure to justify any generalization. There are instances in which goitre apparently has been introduced into localities where hitherto it had been unknown. McCarrison tells of a village in the foot-hills of the Himalayas where this disease was unknown until a goitrous family came to live in it. Within seven or eight years there were in this village of 1,500, 31 cases of goitre, 29 of which were in people under sixteen years of age, the majority being boys. According to this author, goitre may appear within ten days after a susceptible comes to an endemic area, especially if the newcomer be a young adult. In most instances newcomers to a goitrous district develop the deformity within from six weeks to three months after their arrival. The liability increases, however, with prolonged residence and after six or eight years all newcomers to goitrous districts develop the deformity, provided they were not more than eighteen years old when they came. Susceptibility apparently decreases with age.

In endemic localities there is from time to time marked fluctuation in the intensity of the disease as determined by the proportion of people affected. For some years this proportion grows constantly larger and then follows a period of decline. These increasing and decreasing manifestations are apparently without explanation. Some localities where a few years before a large proportion of the inhabitants was involved, may show so marked a decline that only a few isolated cases are in evidence. Then for some unknown reason the cause, whatever it may be, manifests greater activity. In a study made of the fluctuations in goitre in 60 departments in France it was shown that between the years 1830 and 1865 the endemic had increased in 16, diminished in 17, and remained practically stationary in the remainder. Of the 17 localities in which goitre had diminished, 15 had formerly been among the most goitrous in the whole of France. In many localities in northern Italy formerly highly goitrous, a case is now seldom seen. Speaking of these fluctuations, Ewald says:

“As these observations have been authenticated by reliable investigators and are, moreover, of so simple a nature that error is almost excluded, they acquire great importance for the etiology of goitre, as they show that the primary cause of the disease cannot be a permanent and unchanging condition inherent in the locality concerned,

but must be sought, partially at least, in such conditions as are subject to fluctuations, sometimes augmenting and sometimes declining.”

In all cases there must be some explanation. Marine and Kimball say that many years ago the industry of sheep raising in Michigan was seriously threatened by the wide prevalence of goitre among these animals. The disease was eliminated from this region unconsciously by the supplanting of imported salt by the native product, which contains iodine and bromine, goitre preventing constituents of the food.

It seems desirable that we should go more fully into the prevalence and distribution of endemic goitre in the Western Hemisphere, and especially in the United States and Canada. It seems quite certain that there were goitrous areas in both North and South America among the Indians when the white man first came. In one of the first chronicles concerning Peru (1688) we are informed that there were certain tribes characterized by great bunches hanging from their throats. These goitres were designated by a special name, *papamarca* or *papas*, translated into the English word *dewlaps*, and they were said to be numerous. A more recent (1777) author wrote of goitre as a disease among Indians living in the valleys of the Cordilleras. Gage, writing in 1787, tells of a priest in Mexico who had an enormous goitre, and states that the same deformity was common among men and women of the neighborhood in which the priest lived and that this defect was popularly believed to be due to the drinking water. The prevalence of goitre in Central America, especially in Guatemala and Nicaragua, was recorded by early Spanish writers. The same authorities state that this deformity was highly prevalent in and roundabout Santa Fe.

In Richardson's *Journal of Franklin's Journey to the Shores of the Polar Sea* is the following statement concerning goitre and cretinism at Edmonton:

“A residence of a single year at Edmonton is sufficient to render a family bronchocelous. Many of the goitres acquire great size. Burnt sponge has been tried and found to remove the disease, but an exposure to the same cause immediately reproduces it. A great proportion of the children of women who have goitres, are born idiots, with large heads and the other distinguishing marks of cretins. I could not learn whether it was necessary that both parents should have goitres to produce cretin children; indeed the want of chastity in the halfbreed women would be a bar to the detection of any inference on this head.”

In the winter of 1797-1798, Barton, then a professor in the Medical School of the University of Pennsylvania, made a journey through New York State, in which he observed a striking prevalence of goitre among both the Indians and the settlers. He states that at that time the eastern boundary of the goitrous area was about Little Falls on the Mohawk River, 56 miles west of Albany, and that it extended, varying in degree

in different localities, as far west as Lake Erie. Barton observed this defect to be most prevalent in and about Manlius, where swollen necks were not confined to human beings, but were quite common among sheep and cattle. It seems that horses were less commonly affected. Barton thought that many of the settlers in central and western New York became alarmed at the appearance of goitre and on this account they returned to New England.

Barton makes the following statement:

“Some of the most remarkable cases of the disease are in a Dutch family which lives upon the north side of the Mohawk River, immediately opposite to Old Fort Schuyler. This family consists of a father, a mother, and four or five children. Every one of them is afflicted with the goitre. The swellings occasion some of them to look hideous. This family removed from the river below this, to the place where they now dwell, about 15 years ago, at which time they had nothing of the disease among them.”

Barton did not forget to look for cretinism among these people and was surprised that he did not find it. He says that he heard there were cretins among the Indians farther west in the neighborhood of what is now Sandusky, Ohio. The rarity of cretinism among the Indians, Barton was inclined to attribute to the nomadic habits of these people; in fact, in the goitrous areas visited by Barton there were no settlements occupied by whites or reds for any long period of time. Barton evidently believed, and he was probably right in this belief, that cretinism follows goitre only after several generations. He wrote as follows:

“In Europe, where this disease (goitre) has been known for near 2,000 years, as the observation of Juvenal shows, there has been time sufficient to give rise to cretinism, if a long continuance of time will produce it. In many parts of America, on the contrary, the causes have not had an opportunity of producing all their full effects; for few of those districts in which the goitre is known to exist have been inhabited by the same people during a period of even 200 years. The aboriginal (or rather Indian) inhabitants of North America have ever been distinguished for their rambling disposition. None of the European settlements in America are 300 years old, and many of those in which the goitre is most common are not 40. Some of the most ancient European settlements in the New World are those of Guatemala, Santa Fe, and other parts of the southern countries of North America; and it is in these countries that the goitre is most common. It was common at Sacapula when Gage visited that place in the year 1626; it is still common there. At the village of Iacaltenango, in the neighborhood of Sacapula, it is asserted that every one of the inhabitants has a goitre; and it is certain, that the disease is beginning to excite great alarm in these and other Spanish settlements of America.”

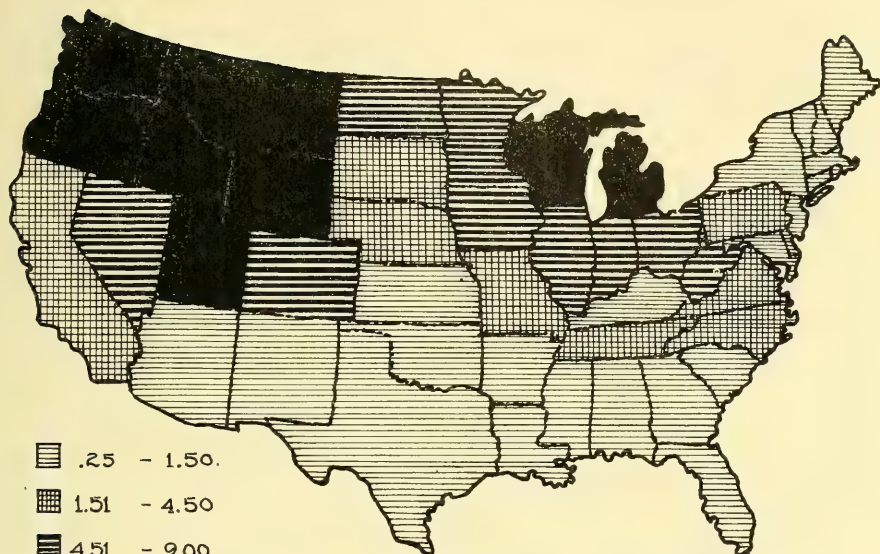
In 1825 Denny wrote concerning the prevalence of goitre in Pittsburgh and vicinity. This author states that goitre was unknown among the Indians and French at the time the latter built and occupied Ft. Duquesne, but that it later became highly prevalent in that region. He wrote as follows:

"In 1798 out of a population of 1,400, 150 were goitrous. In 1806, and for some years thereafter, entire families became goitrous, and the children in one of the common schools were all affected. In the surrounding country the malady was recognized in every direction and sometimes, indeed, in airy and elevated situations, though chiefly on the waters of Chartiers, a branch of the Ohio on the south side, which, in its course to pay the first tribute to that beautiful river, meanders through a rich and early settled valley, bordered by hills of coal. In the town it was most common among the families on the banks of the Monongahela, perhaps from the population beginning in that quarter; but certainly not from the supposed fact, represented to the late Professor Barton, 'that the inhabitants formerly drank the water of the neighboring rivers.' The inhabitants drank well water only, from 1793 to 1806, whilst new cases occurred every year. Now, when the water of the river is substituted by many for the polluted fountains of a crowded city, a recent goitre is unknown. The families on the banks have had wells for the last 30 years. They are sunk nearly to the ordinary level of the Monongahela, yet the water differs from that of the river in its sensible qualities."

Denny states that, among all the goitrous individuals in and about Pittsburgh of that time, he knew of only one case of cretinism, and he says that idiotism was pronounced in this woman before her thyroid gland was appreciably enlarged. This observer was quite convinced that there was some miasmatic exhalation from the coal veins which caused goitre.

During the nineteenth century, from time to time, some progressive physician called attention to the unusual prevalence of goitre throughout the region of the Great Lakes, especially in Ohio, Michigan, and Wisconsin. During the same time, equally observant physicians in various localities of the Northwest, reported on goitre within the areas of their practice. Hrdlicka has called attention, from time to time, to the prevalence of this defect in certain Indian tribes. In 1916 he visited the Cheyenne River and Ft. Yates Sioux.

"The people in question are the Cheyenne River and Ft. Yates Sioux, and were visited by the writer last April. The frequency of goitre among the Cheyenne River bands (Blackfeet and Two Kettle) has been known for many years. In 1908, on the occasion of the writer's report on various diseases among the Indians, they were in that respect at the head of the column, with 61.4 cases of goitre per 1,000 population, compared to three per 1,000 for the United States Indians as a whole. But the present extent and the equally great or even greater frequency of the disease in certain parts of the Ft. Yates territory have not been suspected. * * * The foremost question in this connection is, what are the causes of this localized prevalence of serious disturbances of the thyroid gland. It is not a tribal peculiarity, for other branches of the Sioux away from the river are less affected. There is no evidence that the disease exists for any great distance along the Missouri, or is common among the whites of the same localities. The water used by the natives is mostly that of the Missouri and its small affluents. The present habits of these Indians are those of fairly civilized Indians in general. They were always hunters and great meat eaters, and are doubtless still more so than agricultural tribes, but this is true of all the Sioux. The country is of the rolling prairie type, the climate rigorous but not over severe, malarial infections are infrequent, but scrofula, consumption and venereal diseases prevail; all of which affords no clue as to the causes of the goitre."



▤ .25 - 1.50.

▦ 1.51 - 4.50

▧ 4.51 - 9.00

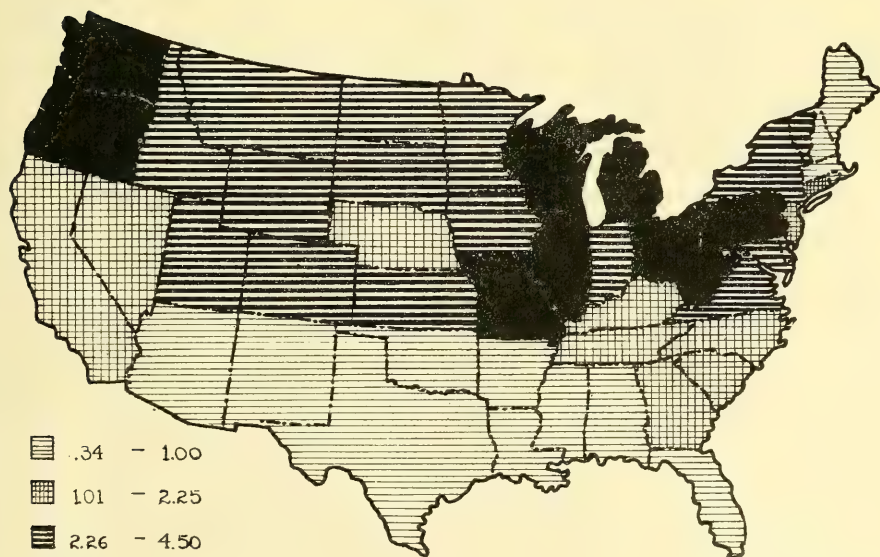
■ 9.01 - 26.91

RATIO PER 1000 MEN
TOTAL, CAMPS AND LOCAL
BOARDS.

SIMPLE GOITRE.

PREVALENCE AMONG DRAFTED MEN
DEFECTS FOUND IN DRAFTED MEN
WAR DEPARTMENT 1920.

Fig. 2.



▤ .34 - 1.00

▦ 1.01 - 2.25

▧ 2.26 - 4.50

■ 4.51 - 9.42

RATIO PER 1000 MEN
TOTAL, CAMPS AND LOCAL
BOARDS.

EXOPHTHALMIC GOITRE.

PREVALENCE AMONG DRAFTED MEN.
DEFECTS FOUND IN DRAFTED MEN
WAR DEPARTMENT 1920.

Fig. 3.

In the examination of draft men upon our entrance into the World War, there was quite a surprise for us in the large number of men found disqualified for military service on account of goitre. It has been generally found where goitre prevails that the number of cases among females is about six times that among males, and still the records of draft boards show that nearly one per cent of the young men examined were unfit for military service on account of goitre. Moreover, these goitrous

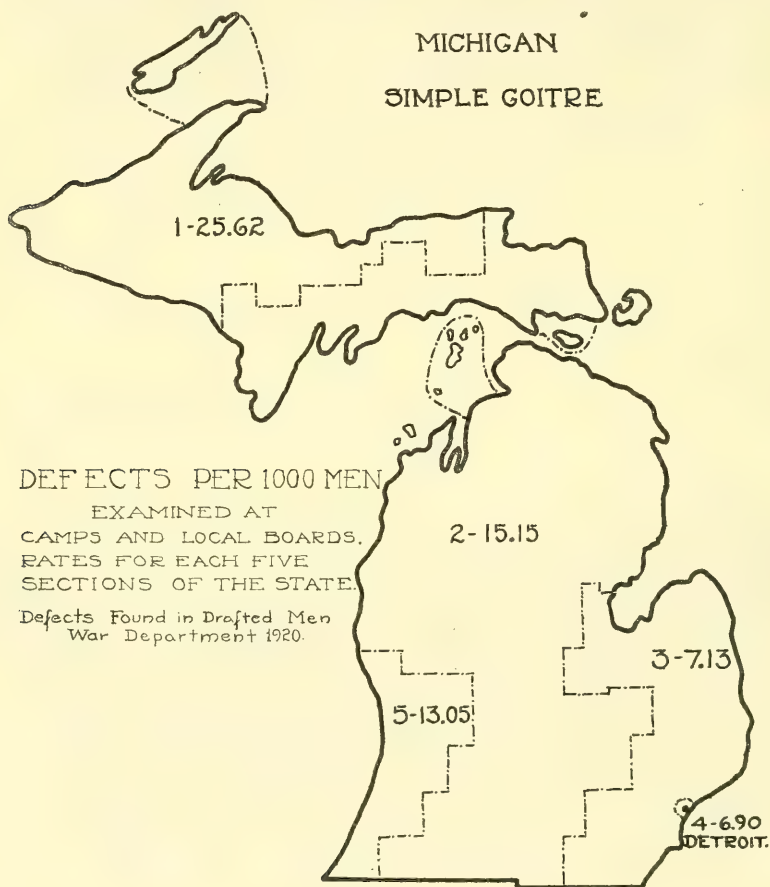


Fig. 4.

men came from certain definite sections of the country. As shown on the map, simple goitre is most common in the northwestern corner of our country, including the states of Washington, Oregon, Montana, Idaho, Wyoming, and Utah. Wisconsin and Michigan also show high rates. It is least frequent in the southern states. Expressed in tabular form by physiographic areas, we observe that simple goitre is 14 times as prevalent in mountain districts as near the seashore. The distribution of

exophthalmic goitre is somewhat different, being less in the desert than in the maritime areas.

TABLE II
GOITRE AMONG DRAFTED MEN

AREA	CASE RATE PER 1,000 MEN	
	SIMPLE	EXOPHTHALMIC
Eastern Manufacturing	1.87	2.28
Mining	9.47	3.10
Desert	2.98	.66
Maritime	.70	1.39
Mountain	10.03	4.67

(“Defects of Drafted Men,” War Dept., 1920, p. 323.)

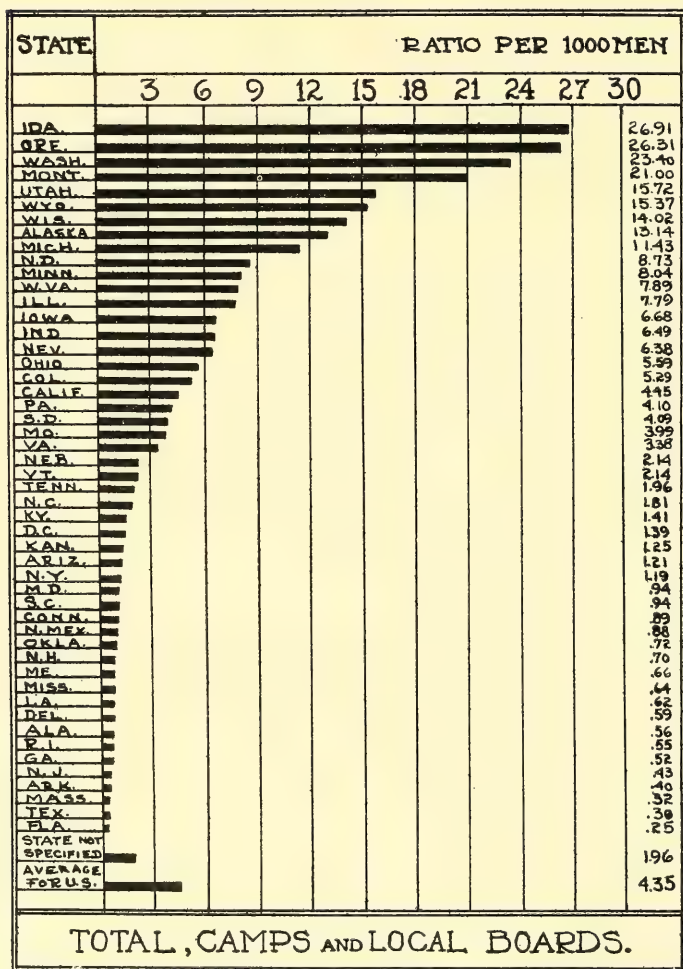
The states of greatest prevalence for exophthalmic goitre are Washington, Wisconsin, Michigan, Oregon, Illinois, Ohio, Pennsylvania, Missouri, and West Virginia. Exophthalmic goitre was 15 times as prevalent in Chicago as in Boston. Evidently there is excellent opportunity for the study of the epidemiology of goitre in this country.

The distribution of simple goitre within a state shows rather wide variation. Thus in Michigan, the City of Detroit shows a ratio of but 6.90 per 1,000, whereas in the northern peninsula the ratio is 25.62. In Section 2 (nonmining area of northern peninsula and whole of central area of southern peninsula) the ratio is 15.15; Section 3 (eastern double range of counties next to Lakes Huron and Erie) 7.13; Section 5 (counties on west side adjacent to Lake Michigan) 13.05; total for the state, 11.30. Certain areas, like those of central and western New York, highly goitrous 100 years ago, are practically free from this defect at the present time. We should be able to determine whether it is the drinking water, and, if so, what constituent of the water is responsible for abnormal metabolism in the thyroid gland.

Hypothyroidism.—In 1873 Gull reported to the Clinical Society of London five cases of a disease the chief characteristics of which were mental apathy and marked edema covering a large part of the body. The title of Gull’s paper is, “A Cretinoid State Supervening in Adult Life in Women.” In 1874 Kocher, of Berne, in reporting cases of complete thyroidectomy, called attention to mental and physical disturbances which in some instances followed this operation. At that time he was not satisfied whether any relation existed between the extirpation of the gland and the subsequent changes in the patient. In 1877 Ord, of London, reported six cases, which he called myxedema, characterized by edematous infiltration of the skin. The cases of both Gull and Ord were all in women. In 1880 Savage reported a case of myxedema in a man, and about the same time Madden called attention to the fact that in all cases of myxedema the thyroid gland is found to be atrophied. During

the eighties of the nineteenth century two eminent Swiss surgeons, Reverdin, of Geneva, and Kocher, of Berne, both of whom were frequently

RATES OF SIMPLE GOITRE BY STATES.



Defects Found In Drafted Men
War Department 1920.

Fig. 5.

removing enlarged thyroids, began to report that in some instances this operation was followed by certain definite signs and symptoms which,

however, were variable in degree. Finally, both of these men were convinced that the development of these untoward conditions is determined by the completeness with which the thyroid gland had been removed. When the extirpation is thorough and there are no accessory thyroid glands which may develop, the myxedematous condition invariably results. However, the extent to which it develops depends upon the age of the individual upon whom the operation has been made. Operative hypothyroidism has supplied much valuable and exact knowledge concerning the function of this gland. When complete thyroidectomy is made upon a child, both the physical and mental development is arrested and, depending upon the age, the child becomes an idiot, an imbecile, or a dullard. When complete thyroidectomy is made upon an adult the untoward symptoms appear more slowly and are never so marked as in childhood. Quite naturally, there can be no arrest of growth because this has already reached its maximum, but even in adults clumsiness in movement, inability to work, incoordination in movement, and mental sluggishness follow. In essence therefore, there is no difference in the effects of operative hypothyroidism on children or adults. The differences are those of degree rather than of kind. The cause in both instances is the same and is due to a suppression of thyroid function. Operative hypothyroidism has been practiced extensively upon domestic animals, especially goats, sheep, rabbits, and dogs, and it has invariably been found that in the adult animal there is arrest and even retrocession of intellectual qualities, and in the young these symptoms are accompanied by arrest in growth. It follows from the observations on operative hypothyroidism in man and experimental hypothyroidism in animals, that the thyroid gland cannot be wholly removed and the body entirely deprived of its function without material deterioration in physical and intellectual development. The investigation has gone further and has shown that after operative or experimental hypothyroidism has been induced the condition of the individual, be it man or beast, may be improved and probably returned to normal, provided that it has not continued too long, either by implanting a thyroid gland or a part of one in some part of the body, or by the administration by mouth of a thyroid gland or some particular preparation made from it.

In 1891 Murray, after studying the effects produced by the entire removal and subsequent implantation of the thyroid gland by Horsley in animals, determined to treat myxedema with an extract of these glands. The first patient upon whom this experiment was made was at that time a woman of forty-six years of age. Her condition was as follows:

“She complains of languor, a disinclination to see strangers, and great sensitiveness

to cold. The temperature is subnormal, and varies between 95.6° and 97.2° in the mouth. The pulse varies between 60 and 70. The face is blank and expressionless and the features are notably thickened. This change is well seen in the *alae nasi* and lips. The subcutaneous connective tissues of the eyelids are so swollen that she finds it difficult to look upwards. There is also considerable swelling beneath the eyes and of the cheeks. The hands and feet are both enlarged; the former have that peculiar shape which has been described as spade-like. The skin is very dry, there is no perspiration, and the superficial layers of the epidermis are continually being shed as a fine white powder. The hair is very fine in texture, and a considerable quantity of it has been lost. She is slow in answering questions; all her actions are slow and are performed with difficulty. The speech is remarkably slow and drawling and the memory is bad. No thyroid gland can be felt in the neck. The urine contains no albumin or sugar."

Murray prepared and administered a glycerin extract of the thyroid gland of a sheep, and three months later the condition of the woman is described as follows:

"The swelling has gradually diminished, and has practically disappeared from the backs of the hands, the skin over them being now loose and freely movable. The lips are much smaller. The swelling of the upper eyelids has diminished so much that she can look upwards quite easily. The swelling beneath the eyes and of the cheeks has also much diminished. The face consequently, as a whole, has gradually improved in appearance and has much more expression, as many of the natural wrinkles, especially about the forehead, have returned. The speech has become more rapid and fluent, the drawl being scarcely noticeable at the present time. She answers questions much more readily, the mind has become more active, and the memory has improved. She is more active in all her movements, and finds that it requires much less effort than formerly to do her housework. She now walks about the streets without any hesitation without a companion. She has menstruated normally during the last six weeks at the regular interval. For the last four weeks the skin has been much less dry and she perspires when walking. The hair remains as before. She is no longer so sensitive to cold. Unfortunately, owing to circumstances a daily record of temperature has not been kept, but out of four observations that have been made lately, about 11 A. M., three times the temperature has been 98.2° and once 97.4° ."

For some time the thyroid extract was administered at intervals of two weeks subcutaneously, twenty-five minims at a time, although during the first three or four weeks this amount was given twice a week. After Mackenzie had shown in 1892 that administration by mouth accomplishes the same purpose, this woman took ten minims by mouth six nights out of each week. In 1918 when it became difficult to obtain glycerin extract she was fed on thyroid tablets. This woman continued in most excellent health until early in 1919 when she developed edema of the lower extremities and died in May of that year at the age of seventy-four from cardiac failure. During the 28 years Murray computes that this woman consumed over nine pints of liquid thyroid extract or its equivalent prepared from the thyroid glands of more than 870 sheep.

Hypothyroidism may result from other conditions than operation and

it may manifest itself in widely varying degrees, depending upon the extent to which the gland fails to perform its functions normally. In the adult, nonoperative hypothyroidism is essentially a chronic disease developing slowly with periods of augmentation and recession, extending often through many years before easily and plainly recognizable symptoms are in evidence. There may or may not be visible or palpable enlargement of the thyroid gland. In the infectious diseases a thyroiditis may be induced and hypothyroidism comes as a sequel. This condition has been observed after pneumonia, malaria, typhoid fever, and possibly other infectious diseases. Cases have been reported in children in which myxedema has followed measles, has continued for years, and after death no trace of thyroid tissue could be found; in other words, the disease had completely deprived the individual of the function of this gland. Spontaneous hypothyroidism, as this form is called, is more frequent in women than in men, especially among women who have borne children rapidly and whose health has been reduced from this cause and subsequent lactation. In writing of this condition, Crotti says:

“The debut of the disease is insidious, slow and progressive. Without apparent cause, more often during the convalescing period of an acute infectious disease, a progressive weakness, physical apathy, and an intellectual torpor, combined with anemia, are observed. The true significance of such conditions, as a rule, is not understood and the patient is treated for anemia. Under medical treatment and rest these conditions are improved or retrocede entirely, but after a few weeks or months they relapse again, and then they follow their slow but progressive course, which may last ten, twenty, or even forty years. In the full development of the disease the face is swollen, the lips are thick and everted, especially the lower one, and the nose and mucous membrane of the nasopharynx are swollen, too. This swelling compels the patient to breathe with open mouth while sleeping, hence causing loud snoring. The tongue is thick, chin plump, and on account of the swelling of the eyelids the eyes seem to be smaller; the cheeks are flabby and the lines of the face have a remarkable immobility; this altogether gives the patient an air of stupidity. His forehead is often wrinkled and his eyebrows are elevated in order to raise the swollen lids above the line of vision. In opposition to what is seen in cardiac and renal diseases, where edema obliterates the wrinkles of the face, in myxedema it exaggerates them. The skin is yellowish white, waxy, with a slight redness on both malar regions. * * * The hands and feet are thick and clumsy, the fingers have the shape of small, round sausages, and move with difficulty; hence the name ‘spade-hands’ of Gull. * * * The symptoms evidenced by the nervous system are very striking. They consist in a weakened memory, slow mental processes, diminution of the capacity of coordination, and diminished activity of the organs of sense and of the reflexes. The patient answers questions slowly and becomes irritable if pressed with them. Although he may usually be of a gentle disposition, he will at times show remarkable bursts of rage. Any mental or physical exertion is a burden to him; his speech is slow, but not stammering or monosyllabic. His slowness is due to a slow process of ideation. His voice is more or less husky on account of the edema of the laryngeal mucous membrane. The organs of special sense are quite often affected; hearing, sight, taste and the sense of smell are diminished. Deaf-

ness, to a greater or less degree, is common, and it is not only due to infiltration of the mucous membrane, but also seems to be of central origin."

Spontaneous infantile hypothyroidism is more frequent than its adult manifestations. In its effects upon the child much depends upon the age at which the thyroid gland ceases to normally supply the products needed by the body. The gland is always present but it may be either hypertrophied or atrophied. The condition of the individual is not determined by the size of the gland but by the extent to which it functions. It is claimed by some that these cases are due to infection through the placenta, while others hold that the cause of this condition lies in some nutritional disturbance. As a rule, or at least in fifty per cent of cases, there is some enlargement of the maternal thyroid during pregnancy and this enlargement is accompanied by evidence of increased elaboration of thyroid products. Apparently, the pregnant woman must supply thyroid hormones not only for her own metabolic processes, but also for those upon which the growth of the fetus depends. Tuberculosis, syphilis, and alcoholism in the mother have been accused of being responsible for hypothyroidism in the infant.

Cretinism.—This distressing condition is due to congenital hypothyroidism and the failure to function on the part of the thyroid may be partial or complete. When the condition physiologically is one of athyroidism there is no physical or mental development of the child. It is believed that every cretin is born of parents one or both of whom has a goitre. The relation between hypothyroidism in parents and cretinism in the offspring certainly admits of no dispute and has been recognized as an established fact by all who have investigated this matter. Fodéré wrote: "Goitre is only the first degree of a degeneration whose last manifestation is cretinism." Fabre said: "Goitre is the parent of cretinism." Morel is authority for the dictum: "One develops goitre, one is born a cretin." The report of the Sardinian Commission to study goitre and cretinism contains the following statement:

"Cretinism does not behave like the hereditary diseases inasmuch as it is not the predisposition to cretinism but it is cretinism itself which is transmitted from parents to offspring."

Hirsch, after a most extensive study of the literature of goitre and cretinism, wrote:

"In the whole of the extensive literature of cretinism there is not a single case to be found in which a child born of parents free from goitre or cretinism, and in a locality exempt from them, has become cretinous on being brought in infancy or youth to live in a cretinous region."

When the athyroidism is congenital, the child is usually short lived, death occurring as a rule before the completion of the third year. There

are, however, exceptions, and some endemic cretins have been known to live to extreme old age. The life of such an individual is purely vegetative. He has not even the instinct of self-preservation, or the intelligence to take food when it is placed within his reach. He does not recognize even his parents and neither resents unkindness nor appreciates favors. When the hypothyroidism does not become extreme until the child has undergone some mental and physical development, the condition is not quite so bad and depends upon the development reached before the thyroid gland failed utterly to supply its essential products. It will be seen from this that cretins differ in degree one from the other, and it is customary to distinguish between cretins and cretinoids. In the newborn normal child it is impossible to tell what the developed mental processes of the future are to be. During the first weeks of life every child leads what may be called a vegetative existence. The normal child gradually grows out of this, both physically and mentally, while the cretinous child remains in the vegetative state. It is the opinion of some that during the period of lactation the milk of the mother supplies the infant with a small and insufficient amount of thyroid hormone. This view is supported by the fact that the evidences of cretinism may not be noticeable until after the child is weaned. The cretin remains a child as long as it lives, but it must not be supposed that all dwarfs are cretins. As is well known, there are dwarfs who are fairly active, both physically and intellectually. This form of dwarfism has no connection with cretinism. Cretinism must also be distinguished from infantilism, mongolism, microcephalia, and hydrocephalia.

As is the case with endemic goitre, there are marked fluctuations in the production of cretins in localities. On the whole, it can be said that both endemic goitre and cretinism are decreasing in most parts of Europe. According to Kutschera, in 1861 there was one cretin for every 167 inhabitants of Styria, while in 1912 there was one to every 539. Both conditions have disappeared from certain localized areas in Styria where they were once common. There is an impression among those who have studied endemic areas that on the whole there has been not only a diminution in the number of cases, but also a marked decline in the severity of the manifestations of the symptoms of hypothyroidism.

We have already remarked upon the rarity of cretinism, even in goitrous areas, in America. There is a belief among those who have studied this subject, that there must be several generations of goitrous ancestors before cretinism appears with any degree of frequency in a given community. Although, as we have seen, there are certain well-marked goitrous areas in the United States, even in these, cretinism is rare and this possibly may be due, in the first place to the normal nomadic

habits of the Indians, and the scarcely less striking migratory tendencies among the whites.

Hyperthyroidism.—Parry in 1825, Graves in 1835, and Basedow in 1842, called attention to a disease which has since been known among English speaking people as Graves' disease and among the Germans as Basedow's disease, and which is now best designated a hyperthyroidism. The gland is usually enlarged, though it may be quite normal in size, and in rare instances it is small. Anatomic development, in this case at least, usually precedes or accompanies overproduction of thyroid secretions, but this is not always true. It is by the symptoms rather than by the size of the gland that we are to determine the existence of this disease. The symptoms are quite the opposite of those of hypothyroidism. The processes of life as they are influenced by the secretion of the thyroid gland proceed with undue rapidity. It is not within the province of a work on epidemiology to go into detail concerning the symptoms of this disease. It may be well, however, to recall some of the most important facts. The pulse is accelerated and is liable to many irregularities, most of which are supposed to be due to influences coming from the central nervous system, although they are to some extent recognized as varying with the respiration. Palpitation is in some cases most distressing. The patient feels his heart beating very forcefully and irregularly against his chest wall. This condition is increased by exercise, by nervous excitement, and by indulging in any form of stimulation. In most cases there is protrusion of the eyeballs, completing the triad of symptoms which characterizes the symptom-complex of Graves' disease; thyroid hypertrophy, tachycardia, and exophthalmos. Mentally, the individual is quite constantly at high tension, restless, and apprehensive. Muscular tremor is one of the earliest symptoms and may be localized or general, easily recognizable by the mere passer-by or known only to the patient himself. This tremor is not pathognomonic of Graves' disease, but it is an important symptom. The restlessness is accompanied by marked muscular fatigue, especially when exercise is accompanied by mental excitement. The psychoses of hyperthyroidism are many and varied, manifesting themselves in restlessness, instability, irritability, and emotional outbursts. A patient suffering from this disease is very much in the condition of a normal individual laboring under great excitement. It has been defined in its worst forms as a condition of chronic terror or fright; indeed, there are those who would make fright a chief factor in the causation of hyperthyroidism. Bram has assembled from the literature sufficient evidence, in his opinion, to make it quite certain that the majority of cases reported as shell shock during the World

War were in reality instances of hyperthyroidism. Southard, in his detailed studies of 589 cases of shell shock, says:

“Hyperthyroidism itself has been, of course, a rather striking feature in the foreground or background of many sick patients in the war.”

It is certainly true that even mild hyperthyroidism should exclude any man from military service, but we do not believe that this condition was an important factor in the causation of that medley of nervous disorders so frequently seen in all the armies in the late war and we do not believe that Southard intended to make this impression, for in another place he says:

“This soldier’s heart is sometimes associated with hyperthyroidism, sometimes hyperthyroidism is found alone, with symptoms suggesting those of a sort of diffuse shell shock.”

An army of hyperthyroids in a state of chronic fright would not long hesitate should the choice lie between flight and fight; indeed, Sigaud gives an historical example when he tells that Brazilian soldiers, having reached a goitrous area, took to flight in terror as their thyroids enlarged.

Sometimes hyperthyroidism is followed by hypothyroidism, the individual passing by degrees from a state of muscular nervous excitability into one of sluggishness in movement and mental hebetude, and occasionally with myxedema. This transformation is easily understood. The cells of the gland wear themselves out at the high rate at which they have been going, degenerate and become incapable of supplying the normal needs of the body. There is another condition which sometimes makes itself manifest in the progress of hyperthyroidism, and this is not so easily explained. A patient with Graves’ disease may manifest mingled symptoms of hyperthyroidism and hypothyroidism. This condition is best designated as dysthyroidism and the only explanation that can be offered at present is that the functions of the thyroid glands are multiple, and one function may be overworking while the other is falling below the normal level.

Soon after the recognition of the importance of the thyroid gland and its secretions in health and in disease, some physicians began to attribute all the ills to which flesh is heir to disordered thyroid activity, and especially to lack of proper activity on the part of this organ. Consequently, they administered thyroid-gland tablets in all diseases, or at least in many. For a time this therapeutic measure became exceedingly popular in attempts to reduce obesity. It did not take long to accumulate in medical literature sufficient evidence that this is a practice not devoid of danger. One man took a thousand five-grain tablets of thyroid in a few weeks and developed typical Graves’ disease, with enlargement of

the gland, tremor and exophthalmos. A woman took six or eight tablets a day for two months. She lost about 16 pounds, but she developed insomnia, vertigo, palpitation, and had hallucinations. One enterprising student, with the idea of testing it out upon himself, ate from six to eight sheep thyroids daily for eight days, at the end of which time he had marked tremor, violent palpitation, and developed a condition of delirium. Another medical student took daily for two weeks one lobe of the thyroid of sheep and developed tremor so extensively that he could not feed himself, and this condition was accompanied by palpitation and exophthalmos. These rash experiments have not been without their value, inasmuch as from them we have received further confirmation that Graves' disease is essentially one of hyperthyroidism. This fact has furthermore been confirmed by the demonstration that hyperthyroidism, with enlargement of the gland, may be brought about by excessive medication with iodine and preparations containing this element. Even the too free application of tincture of iodine to the thyroid gland has been known to have a like effect.

Iodine in the Thyroid.—Soon after the discovery of iodine by Courtois (1812) and the more thorough study by Davy, this element was taken up by the medical profession and in a short time the tincture was being applied to all kinds of tumors, especially noninflammatory growths. There seems to have been an impression made upon the medical profession early that iodine, either in the form of the tincture or as some binary salt, has a place in the treatment of goitre. In 1895 Baumann found traces of this element in various organs of the human body, but found it more abundantly in the thyroid gland. This greatly increased interest in the probability that iodine might be concerned in some way in the growth and function of the thyroid. Since that time chemists have been busy in looking for iodine in this gland, in determining the amount present, and in trying to ascertain the form in which this element exists in the gland. Numerous organic substances containing iodine have been prepared from thyroid tissue. Some of these have been highly complex protein substances and have been given different names by their discoverers. Baumann called his preparation thyroiodine or iodothyron; Oswald named his product iodothyro-globulin, and others have had the satisfaction of christening their products to suit their fancy. About 1914 Kendall obtained from the thyroid gland a crystalline organic substance containing sixty per cent of iodine. Kendall has worked out a formula and believes this substance to be di-iodo-di-hydroxy-indol, and of its action he makes the following statement:

“The entire activity of the thyroid is manifested by the administration of alpha-iodine, a crystalline compound, alone. There appears to be no other substance in the thyroid secretion which acts directly. This substance, given even in very small amounts,

will supplant thyroid activity, relieving the conditions of myxedema and cretinism, and in excess will produce symptoms simulating exophthalmic goitre. It appears to have no direct action on the pulse rate. The extent to which the pulse rate is affected depends not on the administration of the thyroid (hormone), but on the simultaneous ingestion of food and in particular of amino acids. This effect may be outlined as follows: after the administration of the compound there is no apparent effect for many hours. There is no increased pulse rate or drop in blood pressure. However, if thyroid hormone and amino acids are injected simultaneously, the pulse rate is enormously affected, and even death may result, due to the apparently great increase in metabolism going on in the animal. It appears very probable that the thyroid hormone manifests its activity in some way with amino acids.''

That iodine does affect the function of the thyroid there can be but little if any doubt. Chemists have piled up long tables showing the percentages of iodine in normal thyroids at various ages and in every recognizable abnormality of this organ. These percentage determinations are of but little value. An enlarged thyroid is likely to show but a small percentage of the iodine constituent and still it may do its work fairly well or very unsatisfactorily. The larger part of such a gland may consist of abnormal growth and this, of course, would decrease the percentage of iodine in the whole gland, while its functioning part may contain a normal supply. We think it can be said with a fair degree of certainty that the human body needs in its food for the proper function of the thyroid gland, at least a minimum amount of iodine-containing substances. These are found most abundantly in such foods as fish, mushrooms, the legumes, and roots; and in such greens as asparagus and spinach. In hypothyroidism some increase in the administration of iodine is for the most part beneficial, while in hyperthyroidism it is harmful; in short, it is a two-edged sword, and in our opinion, iodine in any form should not be used in the prevention or treatment of goitre except under rather close medical supervision. McClendon, who seems to accept the iodine-deficiency theory, suggests that a salt preparation containing iodine might be made from sea water and the substitution of this for the iodine-free salt now in general use in this country might greatly reduce cases of goitre.

Etiology.—From remote times there has been an idea that goitre and cretinism are in some way due to drinking water. Even in the classical legends there are wonderful stories about the effects induced by drinking the waters of certain springs, wells, and rivers. We are told that on the Island of Chios there was a well, above which was a warning that the drinking of its waters would render men stupid and dull. There is a story of a similar well in Beotia and a like legend concerning the Red Well in Ethiopia and the Gallus River in Phrygia. Ovid wrote that there are rivers whose waters affect not the body so much as the mind. Pliny goes into some detail concerning the bad effects that may follow

the drinking of certain waters in the Apennines, as well as those of Crete, Chios, and Phrygia. Vitruvius tells of a people inhabiting an Alpine valley who have goitre on account of the water which they drink. Agricola writes of a well in the Alps, the drinking of the waters of which affects the brain and makes the drinkers stupid. The River Struma in the Balkans owes its name to the fact that the people living along its banks are goitrous and cretinous. It is a popular belief in Alpine regions that the drinking of the waters of certain wells and springs will induce goitre, and we are told that it is the custom of young men to resort to these sources in order to develop goitre and thus secure exemption from military service. This belief of the relation between the drinking water and endemic goitre has come down through all recorded time and apparently is met with in both hemispheres.

Paracelsus believed that water induces goitre by virtue of its mineral constituents. This view was largely accepted for centuries, and at first it was believed to be the lime in the water which is accountable for the enlargement of the gland. This theory was modified and for a time it was held that the active agent in limestone is magnesia. It was argued that all places where goitre is endemic are situated on limestone formations and that magnesia is an essential constituent of the limestone, but more extensive investigation and a more thorough geological study of endemic areas showed that limestone either with or without magnesia is not essential to an endemic area. Certain of these areas are located upon eruptive rocks. Other mineral constituents of earth and water to which goitre has been attributed are metals, sulphur, iodine, and common salt. With regard to iodine, the view was held by Chatin that water will cause goitre and cretinism when it contains no trace of this element. This investigator (about 1850) cited many waters, both in endemic areas and in places where there is no goitre. He reported a large amount of this element in the waters of the Seine, Yonne, and other rivers in central and western France where there is no endemic goitre. In the Rhone Valley the amount of iodine in the water he found to be much smaller and at the same time some goitre, while in the cretinous localities of Tarentaise and Maurienne the water is free from iodine and the region characterized by the large number of goitrous inhabitants. Others have gone over the same regions and have reported quite differently as the result of their observations; indeed, Bebert found considerable amounts of iodine in the springs in the Valley of Maurienne where goitre and cretinism were at that time widely prevalent. On the other hand, Saint-Lager found an unusually large amount of iodine in a notorious goitre-well at Beaulieu. Similar studies of the relation between iodine in the water and the presence of goitre in widely separated parts of the world seem

to show that there can be no relation between the absence of iodine in the drinking water and the prevalence of endemic goitre and cretinism.

It has been held that water free from common salt may cause goitre. This is in accord with the theory that snow water and melted ice cause enlargement of the thyroid.

One of the most recent theories as to the relation between drinking water and endemic goitre is that offered by Repin, who holds that goitrogenous waters are determined by the presence of radio-active substances. Hesse has investigated this matter in Saxony and adjacent parts of Bohemia where some of the most radio-active springs in the world are located, and finds that there is no relation, unless it be an accidental one, between the prevalence of goitre and the use of radio-active waters. Up to the present time every attempt to show a relation between inorganic constituents of drinking water and the prevalence of goitre has proved unsatisfactory.

The Birchers (father and son) have long carried out a series of experiments upon the production of goitre in animals by drinking water. They believe that goitre occurs only where the rocks were formed by marine deposits and that where the rocks are eruptive and where they were formed as fresh-water deposits, there is no goitre. They state that goitre is highly prevalent among the villages situated on the right bank of the River Aar where the soil formation is made up of marine deposits, while on the left bank of the river there is no goitre and the formation is either crystalline or fresh-water deposits. They had an idea that there are in the rocks certain colloidal substances which may be dissolved in water and which are responsible for goitre. They took a cubic meter of rock from the goitrous area and placed the rock in a wooden box which they filled with distilled water, and after allowing this to stand for some days it was given to rats. These animals after about nine months developed goitre. Further, they demonstrated, apparently at least, that filtration through a Berkefeld does not remove the goitrogenous substances, while dialysis through parchment does. They were not able to induce goitre in rats with water which had passed through the dialyzer, but did produce goitre in animals fed upon the substances collected on the dialyzer. Since the goitrogenous substance does not pass through a membrane, these investigators claimed that it must be colloidal. They furthermore found that waters from goitrogenous springs may be deprived of their active constituents by centrifugation. Further investigation showed that the goitrogenous substance may be removed from water by filtration through a layer of powdered charcoal 30 centimeters thick. The addition to the water of zinc hydrate causes a precipitation and renders the supernatant fluid innocuous. An ultramicroscopic examination of goitrous waters shows a large number of particles of slightly

oval shape and showing continuous movement. These investigators, at least in their last report, express no opinion as to the exact nature of this colloidal substance. Kocher dissents from the Bircher findings. He and his assistants examined more than 75,000 school children in Switzerland between seven and fifteen years of age and found that in some parts of the Bernese Oberland from eighty to ninety per cent had goitre. While, according to Kocher's finding, goitre is much more frequent upon marine formations, as claimed by Bircher, crystalline and fresh-water formations are by no means free from it. Kocher reached the conclusion that the goitrogenous principle is not determined by the mineralogical or constitutional character of the soil, but by its comparative pollution. In Saxony, Hesse was able to substantiate the Bircher theory, although he found that endemic goitre was more prevalent upon the earliest strata of marine sedimentation. Investigations in Lower Franconia seem to agree quite fully with the theories of Bircher; indeed, Lobenhoffer, who conducted studies in Franconia, thinks that the presence or absence of endemic goitre is a true index of the geological formation and that when apparent contradictions are found it will be proved that a mistake has been made in the geological studies. Schittenhelm and Weichardt, carrying on investigations in Bavaria, reached the conclusion that one and the same rock formation may support goitrous or nongoitrous areas. They come to the conclusion that the existence or nonexistence of goitre in a given locality is dependent upon infection through pollution of the water.

Wilms suggests that goitre may be due to an organic substance of fossil origin. It is generally agreed among those who have investigated this subject that cistern water does not induce goitre; that boiling well, spring, or river water renders it innocuous, and that filtration through porcelain renders the water less likely to cause goitre.

The water theory has been tested out by Marine and Lenhart on fish at a large private hatchery in the mountains of Pennsylvania. The trout stream originates in a spring some distance above the first pond or tank. Fish living in the stream above the tanks were free from goitre. The water from this stream flows from Tank No. 1 through Tank 19 without any fresh accession. The percentage of goitre cases in the tanks increased from Nos. 1 to 19. The water leaving No. 19 flows in an open stream for some distance and receives fresh water from another spring before it reaches Tank 20. Tank 20 receives about three times the amount of water that Tank 19 does and has the advantages of an additional fresh supply. The water from No. 20 flows from tank to tank until it discharges from No. 36 into an open pond. The fish in this pond, which is the receptacle of the water from all the tanks, were practically free from goitre. It is supposed that the fish in the pond

below the tanks and which have been transferred from the tanks to the pond have recovered from the goitres which they had while in the tanks. Marine and Lenhart are very careful about expressing their conclusions. They say:

“Direct infection cannot be excluded, but the fact that fish placed in the tailrace recover spontaneously, although living in the theoretically most polluted water, is not in harmony with our present conception of water-borne infection. Taking up the metabolic theory, the three factors of overfeeding, overcrowding, and limited proportional water-supply together with the many possibilities into which they are divisible seem to us to be in some way, still obscure, directly concerned with the development of the disease. It is not probable that a single substance, whether the result of food decomposition or of excretory products, excites the thyroid to its activity but rather that the thyroid reaction is the result of the activity of a great variety of these products. * * * Overfeeding and overcrowding and a limited water-supply are the three major factors in the production of filthy, unhygienic tanks or ponds and these insatiable, unhygienic, filthy tanks are in a very important but still unknown manner associated with the development of thyroid hyperplasia.”

It was found that the placing of a very small quantity of iodine (1-5,000,000) in the water of the tank led to the disappearance of the goitres of the fish in that tank.

Infection Theory.—Hirsch sums up his opinion as follows:

“The absence of results to all these inquiries about the genesis of goitre and cretinism—inquiries which have extended to every influence perceptible to the senses that could be brought into the consideration of the question before us—warrants, I will not say compels, the conclusion that in those diseases we have to do with a specific agent, a *veritable morbid poison*, and that endemic goitre and cretinism *have to be reckoned among the infective diseases*. This doctrine finds a certain support in two things; on the one hand the fluctuations in the amount of the sickness, which we have had frequently occasion to notice, and for which there is no sufficient explanation to be found in the states of the atmosphere or of the soil or of hygiene; on the other hand, the epidemic outbreaks of goitre, for which the theory of infection, as Saillard, Viry and Richard, Thibaud and other French military surgeons have recognized and said, is hitherto the only one that affords an explanation, and an explanation that accords most nearly with the facts of the case. * * * As to the nature of this goitrous and cretinous virus, and its means of conveyance, it is impossible to form a well-grounded opinion. Its existence and development would appear to depend upon certain definite kinds of soil, such as a soil containing dolomite rock, and it would appear to occur principally in water, perhaps associated also in some circumstances with plants or suspended in the air. Whether its nature is organic or inorganic is a question that evades our answering.”

Recently McCarrison, who for years has been an earnest and a productive investigator of the cause of goitre and cretinism, has concluded that neither chemical constituents of the water, geological peculiarities of the soil, nor factors of nutrition, are primarily responsible for the genesis of this disease. He holds that endemic goitre is due to a living micro-organism and he founds his belief upon the following experimental and observational data: (1) In villages situated upon a polluted mountain

stream there is a steady increase in the prevalence of goitre as one goes down the stream, corresponding with increased pollution of the water. (2) Goitre is produced in the human subject experimentally when the material collected on a Berkefeld by the filtration of goitrogenous water is fed to the individual. Suspending this material in water and boiling it renders it innocuous. Filtration through a Berkefeld only partly deprives the water of its goitrogenous properties. The incubation period in experimental goitre in man averages from 13 to 15 days. (3) The goitrous condition in man is much improved by the administration of intestinal antiseptics, such as thymol. This germicide is given in suspension much as it is in the treatment of hookworm infection, and abstention from alcohol or other substances which dissolve the thymol is essential. It is the opinion of McCarrison that the organism which causes goitre grows and multiplies in the intestine, where it elaborates its poisonous products which are absorbed and have a deleterious effect on the thyroid gland. Furthermore, according to his experience, goitre is benefited by feeding the individual upon milk soured with the Bulgarian bacillus. It is supposed that in this instance the beneficial effects are due to the destructive action of the milk bacillus on the organism which elaborates the goitre-producing poisons. (4) The relief of constipation, thorough purging, and Lane's operation are beneficial in the treatment of goitre. (5) McCarrison lays considerable stress upon the fish experiments, already reported as having been made by Marine and Lenhart, and thinks that these support his ideas of an intestinal toxemia and of the transmission of the organism through the water. (6) Dwelling further upon the fish experiments, McCarrison says that the scrapings from the walls and bottoms of the fish tanks when administered to dogs and rats induce goitre. He states that he has produced goitre experimentally in man by this method of procedure. (7) McCarrison states that he has produced goitre in goats and rats by feeding them upon the fecal material obtained from both goitrous and nongoitrous subjects living in an endemic area. (8) McCarrison states that he has produced goitre experimentally in goats and rats by feeding them upon mixed bacterial cultures obtained from the feces of goitrous and nongoitrous persons. He has grown these cultures under both aerobic and anaerobic conditions and finds that the latter are more potent in the production of goitre. (9) McCarrison finds that when pregnant rats are fed upon these cultures their young will have congenital goitre or be cretinous. (10) Goitres are improved by vaccines made from these mixed cultures. It will be understood that up to his last report McCarrison does not claim to have isolated the specific bacterial organism to which goitre is due. In our opinion, he rather invalidates his statement by the claim that goitre is benefited by vaccines made not only from feces, but also from cultures

of the staphylococcus. It should be understood that it is not McCarri-son's idea that the supposedly guilty bacteria find their way through the intestinal wall and reach the thyroid gland; on the contrary, he plainly states that the goitrous thyroid in endemic localities is invariably sterile. It may be that this investigator is on the road to the complete and satisfactory solution of this question which has perplexed epidemiologists through centuries. With us however, there is one criticism and one reason why, at present at least, we cannot fully accept his conclusions. All his experiments have been made in goitrous localities. In order to do him full justice, however, we make the following quotation from one of his most recent reports:

"These organisms reach the alimentary tract of man and animals by means of infected soil, food, or water, and there they flourish and produce toxins which, on absorption into the blood stream, initiate the goitrous changes in the thyroid gland. Soil, water, and food are, therefore, vehicles only whereby the infecting agent or agents reach the body of men and animals. It seems almost certain that the great source of the disease is the infected individual, and that he is the producer, the reservoir and the distributor or carrier of the infecting agents. The agents are discharged from the body in the feces, and it may be in other ways not known to us, as, for example, in the urine and saliva. If they reach a damp soil containing a high proportion of organic matter, they live, and it may be, multiply; while if they reach an organically impure and stagnant water which is protected from the purifying effects of light and air, as in the case of many wells (goitrous wells), they may survive for a considerable time.

"All the evidence at present available points to these as the common modes of infection; but there may be other means whereby the living excitants of the disease are conveyed from the sick to the healthy. It is possible, for example, that flies may act as the conveyors of the infection to man. There is no evidence at present available to suggest that any ectoparasite, biting insect, or worm acts as a host for the further development of the living excitant of endemic goitre outside the body of man and animals. The very wide distribution of the disease in the animal kingdom renders such a mode of spread improbable. In their manner of origin and spread, endemic goitre and typhoid fever closely resemble one another. The conditions which are favorable to the development and spread of one are equally favorable to the other."

Theory of Contact.—There are students of the epidemiology of goitre and cretinism who believe that all the stories about goitrous wells, springs, and rivers are mythical, that water is not the carrier of the goitrogenous substance, and that the disease is acquired only through intimate personal contact. The men who teach this doctrine are, for the most part, Austrians, and the most notable among these are Kutschera and Tausig, although on some minor details they are not in entire accord. These men hold that, while goitre is a place disease, it is more than that; it is a house disease. They also use the fish experiments in support of their views and greatly stress overcrowding and intimate contact. In support of these views they give numerous histories, some applicable to animals, some to man, and some including both. The fol-

lowing is an illustration: On June 30, 1911, a bitch belonging to an army officer bore three pups which, on August 7, were found to be goitrous. Every member of the officer's family was free from this deformity, but the cook who had been living in the family for two years had a slight swelling of the thyroid gland, and an orderly who had been in the officer's service for three years had a well-developed goitre which he had hidden from his master previously by his clothing. This orderly had had special charge of the pups, had fed and fondled them. This occurred in a nongoitrous area. These men would class goitre with extragenital syphilis so far as its transmission is concerned. Tausig travels the same road with Kutschera so far as goitre is concerned, but when it comes to cretinism they part company, Tausig holding that cretinism is always congenital. Köstl reports that in the middle of the nineteenth century it was the custom of the noblemen of the Canton of Valais to bring up only the eldest son in the home, while the younger boys were intentionally turned over to cretinous servants and became cretins. This is a statement which we must decline to believe. The customs of the people in what was Bosnia before the War, as reported by Tausig, certainly gave ample opportunity for contact infection.

"The customs of these people are peculiarly favorable for the transmission of disease by contact. The population is almost entirely of the agricultural class whose custom is to prepare and serve their food in a common vessel from which each takes his portion without the formality or the intervention of forks, spoons, or plates. Cups and glasses are likewise rare. The drinking water is kept in an earthenware jar from which all members of the household drink. Beds are almost unknown; every one sleeps on the floor—members of the family side by side, in the same room. These primitive customs are more prevalent in isolated and inaccessible localities, and are always accentuated in the Mohammedan families who cling to their old traditions with obstinate conservatism and accept modern customs with difficulty, whereas, modern hygienic conceptions have been more rapidly absorbed by the Christian population."

In our opinion, the history of goitre in the United States is more in harmony with the theory that this is an infectious disease rather than with any other theory. The known goitrous area one hundred years ago covered central and western New York and southwestern Pennsylvania. There may have been, and probably there was, goitre in the region of the Great Lakes and in the Northwest, as now, but the disappearance of endemic goitre from parts of New York and Pennsylvania can hardly be due to any climatic changes or to modifications in the geological structure and composition of these regions. In the history of this disease we are told of the great prevalence of both goitre and cretinism around Edmonton, in Alberta, a century or more ago. Some three years ago (1918) a Conservation Committee was sent by the Dominion Government to investigate the prevalence of this disease in the Province of Alberta. This Commission failed to find any unusual

number of cases in the Province and the Deputy Minister of Health for that Province in his recent (1921) communication to us confirms this finding.

Many Indian camps and many villages of the early settlers were grossly contaminated with fecal matter. No doubt the water and soil became heavily infected and with improvements in the sanitary conditions, including provision for a pure water-supply, goitre has disappeared very much in the same manner and from similar causes that have led to the disappearance of typhoid fever.

Prevention.—We have already referred to the statement by Marine and Kimball that a change in the salt furnished the sheep in Michigan had relieved these animals of goitre and had saved the sheep raising industry of the state. Furthermore, we have referred to the work of Marine and Lenhart in the fish hatchery in Pennsylvania, where they demonstrated that the addition of a small amount of iodine to the water in the tanks freed the fish from goitre. There is an interesting contribution along the same line by Smith, who states that it has been known for a number of years that a large percentage of sows in some sections of Montana give birth to hairless and otherwise defective young. Smith states (1916) that the loss in Montana amounts to about 1,000,000 pigs annually, and that there are numerous cases of the same disease among horses, sheep and cattle. There are apparently certain areas not only in Montana, but in North and South Dakota, Washington, Idaho, and Minnesota, in which congenital goitre among domestic animals is common. The endemic areas may be small or large and in certain localities the rancher has learned that he will save his pig crop by moving his pregnant sows through only the short distance of a mile or two. For the most part, these endemic areas consist of narrow creek bottoms not more than a half mile wide, while the bench land beyond does not know this infection. Smith states that ninety per cent of the losses in Montana occur in the drainage area of the Yellowstone River and that the endemic area is from 70 to 150 miles wide, is not sharply defined, and contains ranches or groups of ranches where large numbers of hogs are raised and hairless pigs have never been seen. In the fall of 1915 Smith carried 15 sows from a nongoitrous area into an affected district. There he put five in each of three pens. Those in No. 1 had, in addition to their daily food, 15 grains of potassium iodid; those in No. 2 had 5 grains of sheep thyroid, while those in No. 3 had no addition to the ordinary food. Only four of the sows in Pen 3 farrowed, producing 18 pigs. All these were puny and 13 died during the first few days. They were not hairless, but had thin hair and no vitality. The pigs of Groups 1 and 2 were strong and vigorous. In a second experiment, 28 sows on five ranches in endemic areas, were given each five grains of potassium iodid daily.

The sows that had already farrowed on these ranches had produced hairless pigs. Each of the 28 that received the iodid had normal pigs. Smith concludes as follows:

"An iodin deficiency during the gestation period causes a lack of function and hyperplasia of the fetal thyroid, resulting in an arrested development of the fetus. If more iodin were fed to the pregnant animals in large sections of this continent, especially during the winter months, the young that they produce would be more healthy and more vigorous and the large number of weak and defective young animals that are produced annually would be greatly reduced. Fetal athyrosis presents strong evidence that there is a direct relation between the physiologically active constituents of the thyroid and growth of the epidermal appendages. An abundant secretion of the fetal thyroid, during the later stages of intrauterine life, is essential for the normal development of the fetus."

In 1914, Hall examined 3,339 students at the University of the State of Washington with reference to goitre. Of 2,086 males, of an average age of twenty years and five months, 17.93 per cent had enlarged thyroids; of 1,253 women, of an average age of nineteen years and three months, 30.98 per cent showed a like condition. Olsen found among 606 women in Chicago, 17.87 per cent with goitre. Marine and Kimball examined 3,872 girls from the fifth to the twelfth grades inclusive of the public schools in Akron, Ohio. So far as the thyroid is concerned, 43.59 per cent were normal, 49.88 per cent had slightly enlarged thyroids, in 6.35 per cent there was moderate enlargement, in .18 per cent, marked enlargement, and in 1.01 the gland was adenomatous. These figures are actually higher than those found in the Vosges and other eastern parts of France by MacAuliffe, but they are lower than those reported from Bavaria by Schittenhelm and Weichardt.

Examination of school children in Detroit during 1921-22 has shown thyroid, either moderately or markedly enlarged, in 2.9 per cent of 9000 children who were 15 per cent or more underweight. Among 14,000 children of the first grade, 1.2 per cent were discovered with enlarged thyroid. Among a small group of the better schools the percentage among the first graders was 0.3, while in a group of poorer schools it was 1.3 per cent.

Recognizing the wide prevalence of goitre among children in at least certain parts of the United States, Marine and Kimball have recommended that small doses of sodium iodid be routinely administered to the school children, at least those in goitrous areas.

They report the results of two and one-half years' observations in Akron, Ohio. Of 2190 school girls who have taken 2 grams of sodium iodid twice yearly, only five have developed enlargement of the thyroid, while of 2305 pupils not given this prophylactic, 495 have developed enlarged thyroid. Another group of 1182 pupils with thyroid enlargement to begin with were given the sodium iodid, and 773 showed a

decrease in size. In contrast to this is a group of 1,048 with thyroid enlargement, to whom no iodine was given. In this group only 145 thyroids decreased in size. These data open up the possibilities of both preventing and curing thyroid enlargement. These authors were aware of possible effects of overdosing with iodine but concluded that this danger was negligible. No cases of exophthalmic goitre developed. Iodism was noted in eleven cases among the Akron school girls during the two and a half years, but most of these cases were very mild, and the treatment was not stopped. The authors look upon this work as an important public health measure best administered through the schools to pupils between the ages of 11 and 17. They believe that the administration of from 3 to 5 mgs. of iodine twice weekly over a period of a month and repeated twice yearly will answer the purpose. The results of the Akron study are in agreement with those of Klinger in Zurich, Switzerland.

In attempts to improve the conditions in endemic areas, quite naturally water-supplies have received attention. In some localities a change in water-supply has within a few years apparently relieved the entire community of goitre. We must remember, however, that *post hoc* does not always mean *propter hoc*, for, on the other hand, it has happened that the introduction of a supposedly pure water-supply into a goitre-free area has been followed by the development of this deformity among the inhabitants. Examples of both sides of this question have been furnished by the Birchers. In 1885 fifty-nine per cent of the inhabitants of Rupperwil had goitrous growths. In 1886 a water-supply from a goitre-free area in the Jura was provided for Rupperwil. The percentage of goitrous persons in this locality has gradually decreased and the deformity has practically disappeared. A still more striking example is given of the village of Asp. In 1863 this village showed among its inhabitants thirty-four per cent of goitre, eight per cent of cretins, and fifteen per cent of deaf mutes. In 1907 the upper part of this village brought in a new water-supply while the older part continued the former supply. In 1910 the upper village had 6.4 per cent of goitre and the lower village 38 per cent. On the other side, the Birchers cite the community of Desbüren which, having a supply from a nongoitrous area, replaced it by a new supply. This change was followed by an increase in goitre. It will be understood that there is no contradiction in these examples. They show most conclusively that goitre can be reduced or increased by a change in water-supply, but that special attention must be exercised in the selection of the supply. Apart from water-supply, the soil, the houses, the bedding, the garments, and the persons of those living in endemic areas in all probability become contaminated with the virus, whatever it may be, and serve as carriers. As has already been said, there are reasons for

believing that the epidemiology of goitre and cretinism is very much on a par with that of typhoid fever. Our army camps in 1898 were probably soiled as extensively with the typhoid virus as are the endemic areas we are now discussing, with the virus of goitre. At Chickamauga in 1898 the whole area of the Park was polluted with the excreta from typhoid patients. The tentage, blankets, clothing, and persons of the soldiers were soiled with infected material. The geological formation of the Park is closely like that of goitrous areas. The rocks are limestone, tilted and fissured, and consequently furnish easy channels for the flow of water. Springs outside and inside the Park became infected and one could not drink the water of the region, walk over the grounds, rest under a mess tent, or sleep under the blankets of the soldier, without danger of infection. Furthermore, although we have no exact figures bearing upon this point, we have been informed by physicians in Chattanooga that typhoid fever from 1898 down to the present time in the Park and about the Park has shown a higher degree of prevalence than it did before 1898. A like impression is held by physicians at Jacksonville, Fla., and in the neighborhoods of other camps of 1898. We see no reason why goitre and cretinism might not be exterminated from the most highly infected areas. It is a matter of intelligence and energy on the part of the people and of skill and cost for those who undertake to do the work. From the very nature of the disease, the people of endemic areas are not likely to possess enough physical energy and mental alertness necessary to radically improve their condition. The eradication of goitre and cretinism is, in our opinion, even now, wholly possible, but that any great advance in this direction will be made in the near future is not probable, because the initiative must come from the outside and the accomplishment of the task means a cost which but few nations at the present time are in a condition to impose upon themselves.

While we may expect goitre and cretinism to continue in the Alps, Carpathians, and Himalayas, for generations, and possibly for centuries to come, we should realize that in the fairest portions of the earth, including our own land, there are areas, more or less extensive, in which the virus of goitre and cretinism is present and that it tells to some extent at least upon the physical well being and the intellectual development of our children. This is a matter highly suitable for special investigation by boards of health, and what is probably of more importance, the individual practitioner of medicine should be possessed of wider and more exact knowledge on this subject and he should keep his eyes wide open for the recognition of this condition among his patrons and other members of his community. France, Switzerland, Sardinia, Italy, Austria, and other countries where the disease is more in evidence than it

is among us, have from time to time appointed commissions to investigate, ascertain actual facts, and propose methods of improvement. These countries have been driven to this action by distressing conditions already established in certain parts of their territory. The United States, Canada, and England, recognizing that they have goitrous areas, should take steps to improve the conditions in these localities and to protect other portions from the extension of the evil effects of this virus. Its extension is insidious, its progress is slow, but wherever it takes up its residence it demands heavy tribute and holds on with grim pertinacity. It may seem idle to speak so seriously about what is apparently so rare a disease, but, as we have already shown by figures, the percentage of young, in at least certain sections of this country, bearing abnormal thyroid glands, is by no means negligible. Surveys in our schools, like that made by Marine and Kimball at Akron, Ohio, should be extended, and we should at least learn to what extent the thyroid function of the coming generation is likely to be disturbed. With sufficient information we may be justified in following the advice of Marine and Kimball and administer small doses of iodid to our children according to their thyroid needs. If the sheep industry has been saved by an unconscious change in the salt supplied this animal, if it is desirable to protect trout in our hatcheries by the addition of iodine or by feeding them with sea fish, if the protection of our pigs in Montana from congenital goitre has become a serious economic question, then it certainly behooves us to ascertain the exact facts about the prevalence of goitre among our children. If this be a matter of importance, and we think it is, it is the duty of health officers and private physicians to investigate and make report.

Bibliography

- BARTON, B. S.: A Memoir Concerning the Disease of Goitre as it Prevails in Different Parts of North America, Philadelphia, 1800, Way & Groff.
- BRAM, I.: Exophthalmic Goiter and its Non-Surgical Treatment, St. Louis, 1920, C. V. Mosby Company.
- CARREL, A.: Jour. Exper. Med., 1913, vii, 14.
- CROTTI, A.: Thyroid and Thymus, Philadelphia, 1918, Lea & Febiger.
- GUDERNATSCH, J. F.: Am. Jour. Anat., 1913-1914, xv, 431.
- HIRSCH, A.: Geographical Distribution of Disease, London, 1885.
- MARINE, D., AND KIMBALL, O. P.: Jour. Lab. and Clin. Med., 1917, iii, 40.
- MARINE, D., AND LENHART, C. H.: Jour. Exper. Med., 1910, xii, 311.
- MARINE, D., AND ROGOFF, J. M.: Jour. Pharm. and Exper. Therap., 1916, ix, 1.
- MCCARRISON, R.: The Thyroid Gland in Health and Disease, New York, 1917, William Wood & Company.
- MURRAY, G. R.: Brit. Med. Jour., March 13, 1920.
- SMITH, G. E.: Jour. Biol. Chem., 1917, xxix, 215.
- SOUTHARD, E. E.: Shell Shock and Psychiatry, Boston, 1919, W. M. Leonard.
- VINCENT, S.: Internal Secretions and the Ductless Glands, London, 1912, Edward Arnold.

CHAPTER VIII
FOOD POISONING
BROMATOTOXISM

Introduction.—Notwithstanding the fact that man has been daily engaged in making experiments upon himself with foods ever since his earliest Paleolithic ancestors feasted upon their dried herbs, cracked their nuts, and gnawed their bones in their cave dwellings, the subject still remains replete with unsolved problems, and this is a chapter difficult to write. Twenty years ago, after consultation with our classical colleagues, we proposed the word bromatotoxism as the scientific designation for food poisoning; in fact, at that time we suggested the following glossary of new words suitable for use in discussing food poisoning:

Bromatotoxismus, βρωμα (βρώματος), food, and τοξικόν, poison. Food poisoning or poisoning with food.

Bromatotoxicon. A general term for the active agent in a poisonous food.

Bromatotoxin. A basic poison generated in food by the growth of bacteria or fungi.

Galaetotoxismus, γάλα (γάλακτος), milk. Milk poisoning.

Galaetotoxicon.

Galaetotoxin.

Ichthyotoxismus, ἰχθύς, fish. Fish poisoning.

Ichthyotoxicon.

Ichthyotoxin.

Kreotoxismus, κρέας (κρέως), meat. Meat poisoning.

Kreotoxicon.

Kreotoxin.

Mytilotoxismus, μυτίλος, a sea-mussel. Mussel poisoning. Used already by Husemann.

Mytilotoxicon.

Mytilotoxin. The name given by Brieger to the substance discovered by him in poisonous mussel.

Sitotoxismus, σίτος, cereal food. Poisoning with vegetable food.

Sitotoxicon.

Sitotoxin.

Tyrototoxismus, τυρός, cheese. Cheese poisoning. Used already by Husemann.

Tyrototoxicon.

Tyrototoxin.

Husemann uses the word *zoötophotoxismus* to indicate poisoning with animal food. The same author has employed the word *halichthyotoxismus* to designate poisoning with fish. These words have been employed by a few writers on food poisoning since we first suggested them. There is a tendency to make *sitotoxism* equivalent to *bromatotoxism*. This is permissible, but hardly desirable. *Bromatotoxism* means poisoning with any kind of food, vegetable or animal, while *sitotoxism* is best employed to designate poisoning with vegetable food or with grain.

As we have said, a *ptomain* is a basic product of putrefaction and, inasmuch as it has not been demonstrated that the active agent in any poisonous food is such a body, it is manifestly incorrect and improper for a scientific man to use the words "*ptomain poisoning*." In popular parlance this term means any poisonous food. At the present time, in discussing this subject it will be impossible in many instances to distinguish between food poisoning and food infection, or between intoxication and infection. The best we can do is to state the facts so far as we can ascertain them, subject at all times to the corrections which will come with more extended and exact studies.

Sitotoxism.—As is well known, certain plants, ranging from the lowest to the highest, contain substances which are highly poisonous to man and animals. Many of these poisons are alkaloids, such as strychnin, morphin, atropin, etc.; some are glucosides, such as digitalin, saponin, etc., while still others are true toxins, such as are found in castor beans and jequirity beans. Since the discussion of the poisons of plants belongs to botany and toxicology rather than to epidemiology, we omit all discussion of these substances.

Ergotism.—Ergotism is due to poisoning with a fungus known as *Claviceps purpurea*, which develops in the flowers of rye, other grains, and certain wild grasses. It is most frequently found in rye and darnel. Early in the development of the rye flower there may appear in its interior a sweet, unpleasant smelling liquid, which sometimes forms so abundantly that it overflows, runs down upon the stalk, and falls upon the ground. The sugar which it contains attracts ants and other insects, and these aid in the distribution of the fungus. There are certain conditions which are known to favor the development of this parasite. It is more common when there is a rainy spring followed by a hot, dry summer. Thorough cultivation of the soil kills the parasite, and for this reason ergot is more abundant in countries where the soil is not well cultivated. Ergotism has within recent years prevailed in epidemic form only in certain parts of Russia. Grains of ergot, after having been exposed to the air for a few months, lose in large part their toxicity, and consequently epidemics of ergotism follow closely upon the harvests, and especially upon poor harvests, when the parasite is most abundant and the

people are compelled to feed upon what they have without close inquiry as to its quality. It may be pointed out, however, that in the present state of civilization there is but little excuse for the existence of epidemics of ergotism. In the first place, thorough cultivation of the soil would soon completely eradicate this malady, and a proper selection of seed would do much in the same direction. As early as 1858 Kühn pointed out the benefit that would be secured by an early harvesting of fields contaminated with ergot, as by this means the spread and consequent development of this parasite would be largely prevented. Moreover, the ergot grain is much larger than that of rye, and this difference in size permits of the easy separation of the two by means of sieves especially constructed for the purpose. The commercial value of ergot is so much greater than that of rye that the time given to the separation of the two would be profitably spent, and yet so dense is the ignorance and so pronounced is the indolence of certain peasant classes that epidemics of ergotism continue and probably will continue for many years. Kobert and his student, Grünefeld, have found three poisons in ergot; these are, ergotinic acid, sphacelinic acid, and cornutin. The first of these, ergotinic acid, is poisonous when injected subcutaneously or intravenously, but seems to be devoid of harmful properties when taken by mouth; hence it can play no part in the causation of ergotism. It was believed by Kobert that in all cases of ergotism both the sphacelinic acid and the cornutin are active; therefore, a clinical picture of the disease must be a composite resulting from the combined action of the two, and it must vary with the preponderance of one or the other in the ergot taken. According to the same authority, sphacelinic acid is the constituent of ergot that causes gangrene and develops the cachexia of the disease. Grünefeld fed animals with sphacelinic acid and induced gangrene in cocks. The comb, then the wattles, tongue, wings, and crop respectively, were affected. In hogs the ears fell off bit by bit; in horses and cows, the tails, ears, and hoofs separated, while in dogs and cats the gangrene usually began in the skin. When locally applied in concentrated solution, sphacelinic acid causes gangrene of the tissues with which it comes in contact and this explains the necrosis of the living tissue, the ulcerations, and the hemorrhages into the intestines.

Cornutin does not cause death of tissue, but acts directly upon the nervous system and is believed to be the active agent in the causation of ergotismus convulsivus. It acts on the brain and cord, affecting the vagus and vasomotor centers, and acting through the lumbar cord upon the uterus. Cornutin readily undergoes decomposition, gradually losing its virulence, and is found only in fresh ergot, disappearing more quickly than sphacelinic acid. For this reason it happens that those symptoms

due to cornutin are more prominent in outbreaks occurring soon after the harvest, while those due to sphacelinic acid are seen both in early and late epidemics.

Kobert's investigations apparently satisfactorily explained the clinical manifestations and lesions of the two forms of ergotism, but others have not been able to confirm his work and it is reported that he himself worked for years before his death in trying to duplicate the results as above stated, but was unable to do so. More recently, Barger and Dale have found in ergot two highly poisonous bodies, p-hydroxyphenylethylamine and β -iminazoethylamine, but, so far as we can understand, these substances do not fit in so well as did those described by Kobert in the explanation of epidemic ergotism. Pliny, Galen, and other Roman authors, undoubtedly knew something of ergotism and wrote concerning malignant diseases which were due to poisonous grain. During the middle ages ergotism played great havoc from time to time in France. The first recorded epidemic dates as far back as 857 A.D. and, according to Creighton, probably to 590 A.D. This author says:

"Six great outbreaks are recorded in the tenth century, seven in the eleventh, ten in the twelfth, and three in the thirteenth, the medieval series ending with one in the year 1373. The estimates of mortality in the several epidemics of ergotism over a larger or smaller area of France, range as high as 40,000 and 14,000, which numbers may be taken to be the roughest of guesses; but in later times upwards of 500 deaths from ergotism have been accurately counted in a single outbreak within a limited district. The epidemics have been observed in particular seasons, sometimes 20 years or more elapsing without the disease being seen; they have occurred also in particular provinces—in the basin of the Loire, in Lorraine, and since the close of the medieval period, especially in the Sologne. The disease has usually been traced to a spoiled rye crop; but there is undoubted evidence from the more recent period that a poison with corresponding effects can be produced in some other cereals, even in wheat itself."

The ergotism described as existing during the middle ages was of the gangrenous variety. The poison set up endarteritis in the smaller vessels in the extremities, leading to their occlusion and terminating in gangrene. The toes would fall off, then the feet and possibly the legs at the knees, or the process might begin in the fingers, the gangrenous changes gradually ascending, and this was accompanied by an intense burning. The disease at that time was known as *ignis sacer*, or as the fire of St. Anthony, or as *ignis infernalis*. When ergotism began to be reported from Germany it was of quite a different type. It was characterized at first by creeping, itching sensations in the limbs, by spasms of the hands, arms, feet, and legs, often leading to contractures of the joints and in the worst cases terminating in periodic convulsions involving the whole body. It is the difference between the gangrenous and the convulsive forms of this disease which Kobert's investigations apparently so well explained. It seems perfectly reasonable to say that

the ancient French ergotism or the gangrenous form was due to sphacelinic acid while the German or convulsive form was due to the cornutin. According to Kobert's explanation, the difference in time after harvesting when the ergotized rye was eaten would determine, in part at least, whether the disease should be of the gangrenous or the convulsive type. It is within the range of possibility that subsequent investigations may show that there are many and diverse varieties of this parasite and that they are also unlike in their chemical composition, and especially in the poisons which they elaborate and bear.

Creighton has made an analysis of the epidemics in England which might possibly have been due to ergot and has found only one unquestionable instance and this involved only one family and occurred in January, 1762. A peasant family, father, mother, and six children, in Suffolk were attacked with symptoms of gangrenous ergotism, terminating in several of them in the loss of portions of their limbs. This family had not used rye flour, but for some time their bread had been made from damaged wheat, grown in the neighborhood and kept apart from the good grain so as not to spoil it. Other epidemics investigated by Creighton are by no means convincing as to their true nature, and this author concludes that there is no reason for believing that ergotism in either form has ever been widely prevalent in England. He believes this to be due to the fact that the English have never extensively eaten rye bread and that even during the middle ages the cultivation of the soil was more thoroughly done than in France. In the United States there have been rarely, but from time to time, epidemics of ergotism among cattle; but, so far as we know, this disease has never been seen in man in this country either in sporadic or epidemic form.

Lathyrism.—In the second book on epidemics, Hippocrates wrote:

“At Ainos, all men and women, who ate continuously peas, became impotent in the legs and that state persisted.”

From that time to this it has been known that several species of lathyrus or vetch, when constituting a large part of the daily food over a considerable time, may cause certain untoward effects. Three species of lathyrus have been proved to be poisonous under these conditions. They are, *L. sativus*, *L. cicera*, and *L. clymenum*. In countries where and at times when any of these peas constitute a large proportion of the daily diet either for man or domestic animals, symptoms of poisoning result. Of the more than 120 known species of lathyrus, 13 are native of the United States and others are cultivated here on account of their showy flowers, the sweet pea of the garden being an example of the latter. In northern Africa and southern Europe lathyrism has been frequently observed through many centuries, and in India and other parts of Asia it has been and continues to be a cause of severe epidemics.

As early as 1671 it was known that bread made from vetch seeds mixed with Graham flour seriously affected those who ate of it for any length of time and the Grand Duke of Württemberg issued an edict forbidding the use of food of this kind. At that time it was noticed that those who ate of this bread suffered from marked stiffness of the extremities and the disease was regarded as incurable, although death seldom resulted from it. In 1691 Ramazzini described an epidemic in the Grand Duchy of Modena and attributed it to the eating of peas, especially *Ervum*. In 1786 the Government of Florence cautioned the peasants against this danger and during the nineteenth century similar cautions went to the French from their veterinary school of Alfort. Peasants were advised not to feed their horses and other animals too largely on peas. The species to which most French and other European epidemics have been attributed is *L. cicera*. During the latter part of the nineteenth century French army officers in Algeria reported epidemics, large and small, especially among horses. The first report of this disease in modern times from India was made by Sleeman (1834) and concerned an epidemic in the Central Provinces. Subsequent epidemics were reported in the Northwest Provinces by Irving and others. In 1887 the literature upon this subject was collected by Schuchardt. Still more recently, Buchanan has reported epidemics in India, involving, in one instance at least, more than 7,000 cases.

Numerous attempts have been made to isolate the poisonous principle or principles of lathyrus, but, so far, the results obtained have not been altogether satisfactory and to some extent contradictory. Teilleux obtained a resinous body, which, when administered to rabbits in gram doses, caused tetanic movements of the muscles and finally paralysis of the extremities, death occurring within four days. From *Lathyrus cicera*, Bourlier obtained an extract which killed frogs and many small birds within 48 hours at most. An alkaloidal body was obtained by Marie from the seeds of *Lathyrus sativa*; however, this substance when administered subcutaneously to guinea pigs does not induce any of the characteristic symptoms of lathyrism. Astier obtained an alcoholic extract which after repeated injections, induced in dogs complete paraplegia, from which the animals slowly recovered. Recently, 1917, Stockman extracted two kilograms of *L. sativus* grown in India with water acidified with tartaric acid. This extract was precipitated with ninety per cent alcohol, the alcohol removed by distillation and the solution, after being made alkaline with sodium carbonate, was shaken with chloroform. The chloroform on evaporation left an amorphous alkaloid which gave a crystalline salt with hydrochloric acid. The same investigator fed lathyrus to various animals and concludes his investigations as follows:

“(1) Both the large peas (grown on dry wheat lands) and the small peas (grown on wet rice lands) of *Lathyrus sativus* are poisonous. (2) Different samples of peas vary greatly in toxicity. (3) The poisonous substance is an alkaloid. (4) Certain species of animals are very much more susceptible than others. (5) Individual susceptibility varies greatly in the same species. (6) With ordinary samples of the peas and in susceptible animals feeding has to be carried on for some time before toxic symptoms develop. Occasionally, however, the peas seem to be more poisonous and capable of causing more acute poisoning. (7) In monkeys and in other susceptible lower animals prolonged feeding seems to cause a greater or lesser degree of paralysis of the peripheral nerves, along with other symptoms due apparently to an action on the central nervous system. (8) A single large dose of the alkaloid paralyzes the terminations of motor nerves, but other parts of the nervous system are also affected. (9) Histologic examination of the muscles and nervous system in poisoned monkeys showed no structural changes.”

In Hindustani, *L. sativus* is known as khasari, in Bengal as teora, and in the Northwest Provinces as mattar. Stockman, quoting Buchanan, gives the following description of the symptoms in man:

“(1) If a man eats teora for about two months he gets cramps in the calves of his legs, and if he then stops eating the grain he may recover almost entirely, or only a little stiffness of his legs may remain. He is able to walk about without the aid of a stick, but an up and down movement of his shoulders may be noticed when he is walking. His toes may drag slightly on the ground. (2) If he continues eating teora he may experience a somewhat sudden onset of paralysis. If he then stops eating teora he will improve, and in a few weeks he will be able to move about, but with the aid of a long stick. His toes will scrape the ground, and the muscles of the back of his legs will be rigid. (3) If he should still go on eating teora he will lose control over the bladder and rectum sphincters. If he stops eating teora he also will improve, and he will be able to move about after a few months, but he will require to support himself with two sticks. (4) A very small number of cases are unable to stand even with the aid of sticks.”

It is claimed by the Arabs of northern Africa that the poison in peas is destroyed at a high temperature. These people eat vetch prepared in two ways; one preparation, known as “kouskouson” is steamed or boiled, while the other dish, known as “galette” is cooked at a higher temperature, and it is said to be an authenticated fact that injurious effects more frequently follow the use of the former than of the latter. In the same country the first symptom of lathyrism is said to be manifested by a chill which is followed by pain in the loins and legs. A girdle sensation is complained of by some, and motor lameness of the lower extremities is common. The patient walks with difficulty, and later finds locomotion wholly impossible. The knee reflex is greatly intensified and a paresthesia with formication may be marked. It is stated by some that gangrene of the feet and legs may occur, but it is possible that cases upon which this statement is founded were due to ergot poisoning.

Poisoning with bread containing the seeds of darnel (*Lolium temulentum*) has been known and recorded from early Roman times. It is

stated by Orfila that this form of food poisoning played a part in the blockade of Genoa in 1800. More recently, local epidemics have been observed in Europe and India. Cordier took early one morning six drams of the seed and records that this was followed by indistinctness of vision, drowsiness, bodily weakness, nausea, vomiting, tremors of the limbs, and difficulty in speech. Bley has obtained from these seeds a bitter principle which he named loliin, but the action of this substance has not been satisfactorily studied. Freeman attributes the poisonous action of these seeds to a fungus which is frequently found on the seed.

In China certain species of spinach (*Atriplex littoralis* and *A. angustissima*) are supposed to be poisonous. These plants grow up as weeds in the courts, gardens, and along the walls of houses in Peking and they are eaten by poor people, either uncooked or cooked. It has been suggested that the poisonous action of the plant is due to an insect which feeds upon its leaves. According to Laveran, the people who pluck the leaves infect the thumb and forefinger and thus carry the infection to the mouth. This explanation is in accord with the development of the symptoms. The tips of the fingers and the backs of the hands itch and in some instances it is distinctly recognized that the first sensations appear on the thumb and forefinger. These parts become painful, swollen, and cold, and these conditions gradually spread until they may involve the greater part of the body. The eyelids itch, the face is swollen, the nose is cold and markedly cyanosed. The sensation of touch is diminished and ulcers may follow accompanied by much itching and terminating in ugly scars. Gangrene of the fingers has been reported. This looks very much like ergotism.

In Sardinia there occurs from time to time a disease which is believed to be due to the eating of fresh beans (*Vicia fava*) and some go so far as to say that the odor of the blossoms of this plant may cause the untoward symptoms. Fabismus, as it is known, has been studied by a number of most competent investigators, and still the cause has never been satisfactorily explained. Its symptomatology is described by Castellani and Chalmers as follows:

“Within a few hours of eating the beans or of being exposed to the scent of the flowers, an acute febrile attack, associated with marked blood destruction sets in. The red cells fall to 2,000,000 per c.mm., and the hemoglobin to twenty per cent, and icterus sets in with liver tenderness, but no enlargement of that organ or of the spleen. Bile may be vomited and passed in motions, while hemoglobin, urobilin, and indican are found in the urine. Children die in a few days but adults recover quickly.”

The development of skin lesions following the long-continued eating of buckwheat cakes is a rare but well-known phenomenon.

Solanotoxism.—The genus *Solanum* includes a number of herbs and shrubs, some of which are quite highly poisonous. In this genus are the

nightshades, bittersweet, the so-called apple of Sodom, and the common potato. Since the last mentioned is the only member of this genus used as a food, we confine our attention to this. The common potato, designated by us as the Irish potato, contains an alkaloid known as solanin. The presence of this alkaloid in the potato seems to vary greatly, being affected possibly by the soil, and to a greater extent by the condition of the tuber at the time the examination is made. Meyer found in potatoes as ordinarily served, from 0.04 to 0.116 gram per kilo, while young potatoes yielded as much as 0.236 gram per kilo. In potato sprouts and in immature potatoes, Meyer found as much as 0.580 gram per kilo. The danger point seems to be reached when the potato contains as much as 0.2 gram per kilo, although Haselberg found that the isolated alkaloid could be given in much larger doses than this without causing symptoms. Schmiedeberg suggested that the quantity of solanin in potatoes might be increased by the presence of bacteria, and this suggestion was apparently confirmed by studies made by Weil. This is altogether unlikely, and Weil's results have not been confirmed by subsequent investigations. It is still an open question whether potato poisoning is due to the solanin content or to some decomposition product in the food.

Banks reports a family, seven in number, who breakfasted, dined and supped on potatoes, and who began about an hour after breakfast to experience sensations of uneasiness in the stomach and bowels. The potatoes appeared sound and good before they were boiled, but afterwards exhibited black spots and fibers in their structure. The symptoms in all were practically the same and were characterized by evidences of pain, shivering, coldness of the surface, swelling of the abdomen, with excruciating pain on pressure, and distension of the bladder caused by retention. It should be understood that these people were ill for six days before they were carried to hospital. The urine was drawn off and the intestines washed out. The fecal matter thus obtained consisted of large patches of potato peel mixed with spongy balls of decayed woody fiber, in which all traces of structure seemed to have been lost except in the fragments of peel. There was not a trace of starch in the stools and from this matter there was extracted, with ether, an oil which was found to be colorless and volatile. Delirium, the most prominent symptom in poisoning by the solanaceae, was not present. Banks reached the conclusion that a moderate quantity of blighted potatoes might be used without harm if mingled with other articles of aliment, but that they are dangerous when they constitute a large proportion of or are the sole food. All cases recovered, but only after an illness of from four to six weeks. Savage quite wisely suggests that these cases owed their untoward symptoms to the presence of fungi.

Savage reports the only case in England so far as he can find and this

occurred in 1910. The persons involved numbered from 80 to 100 and all had consumed a meal consisting of potatoes and fish fried in oil. As purchased, the potatoes were apparently good and those cooked the evening before did no harm. The second portion was washed and scrubbed and left exposed to ordinary temperature until the following day when they were cooked and eaten. Savage thinks that in all probability the cooking in the oil killed the bacteria but did not alter the bacterial poisons. An outbreak of food poisoning in Glasgow in 1917 is reported by Harris and Cockburn. There were 61 persons involved, with one death in a child five years of age after an illness of 31 hours. In most cases the symptoms continued for only a few hours, but in 10 they lasted from two to three days. Vomiting, diarrhea, and headache, followed by marked debility, were the chief symptoms. Potatoes had been eaten by all those affected. The tubers were normal in appearance but quite a number of them had sprouts, some one-fourth inch in length. The potatoes consumed at this meal contained 0.041 per cent of solanin. Bacteriologic studies gave no results. Harris and Cockburn concluded that the untoward symptoms in this outbreak were due to poisoning with solanin, but Savage does not think this conclusion justified because the symptoms were not those which are induced by this alkaloid. Several epidemics ascribed to potato poisoning have been reported, especially in military garrisons, in Germany. In one of these, Dieudonné isolated from the food, which was a potato salad, *B. proteus*. In pure culture this bacillus had no effect upon mice, but when these animals were fed upon potato cultures of *B. proteus* they died in from 24 to 48 hours. In this outbreak the soldiers were ill two hours after eating the potato salad and all recovered after about seven hours. In another garrison outbreak, Pfuhl estimated that every man who showed symptoms had taken the equivalent of about 0.3 gram of solanin, and he attributed the ill effects to this alkaloid. We agree with Savage that in no case of reported potato poisoning has it been convincingly shown that the active agent has been solanin.

Ichthyotoxism.—There are numerous animals, such as the venomous snakes, scorpions, certain fish, and a number of insects, which have and use for purposes of self-protection poisonous secretions. These are injurious to man when introduced into the body parenterally, but are without action when taken by the mouth, and consequently are not to be discussed in an article on food poisoning.

The flesh of certain animals is known to be poisonous on account of the active agents contained in the plants which they eat. It is stated, and so far as we know, without denial, that in certain sections of this country the flesh of the quail may be injurious to man when this bird has fed upon the mountain laurel. There are probably similar examples,

but this kind of food poisoning is so rare that it needs no discussion. It seems to be pretty well demonstrated that there are found in certain waters fish whose flesh is poisonous. According to Remy, there are in Japan twelve species of fish, all belonging to the genus *Tetrodon*, whose ovaries are poisonous. In winter when these organs are atrophied the fish is less poisonous, although at no time can it be eaten in quantity with impunity. Remy fed dogs upon the ovaries or testicles of these fish caught in winter and found that the animals soon sickened, with salivation, severe and frequent vomiting, and convulsive muscular contractions. A more prompt and more frequently fatal result was obtained when the organs were rubbed up in a mortar and the fluid portion administered subcutaneously. According to Takahaschi and Inoko, this fish poison is highly resistant to prolonged boiling and behaves like a basic substance with the general alkaloidal reagents. It was at one time believed in Japan that beriberi is due to the eating of fish, but the true nature of this disease has been more recently ascertained and is discussed elsewhere.

Petromyzon fluviatilis, which is not classed among fish by modern zoologists, causes, according to Prochorow, a bloody diarrhea, frequently observed in certain districts of Russia. This occurs whether the food is eaten raw or thoroughly cooked, and it is stated that if salt be sprinkled on the animal while it is alive its skin secretes an abundant discharge of mucus and after this the flesh is not poisonous. This may be a fairy story.

Cluppea thrissa and *C. venonosa*, also certain species of *Scarus*, have no poisonous glands, nor are their reproductive organs more poisonous than other parts of the body; still the flesh of these fish is always poisonous. According to Gunther, their harmful properties are due to the medusae, corals, and other decomposing substances upon which they feed. In the West Indies it is a well-known fact that all fish caught off certain coral banks are poisonous and that every part of the animal is unfit for food. The symptoms are those of gastroenteritis, and death frequently results. It has been suggested that ichthyotoxism may be due to substances of vegetable origin which are employed in some countries, notably by savage and partly civilized peoples, to kill fish. That this may be true in some instances is possible, but that this explanation is not generally applicable is shown by the observation that where this method of obtaining fish for food is most frequently employed, no ill results follow, and where it is not resorted to, cases of fish poisoning may be very common. According to Husemann, *Cocculus indicus* has been employed for the purpose of poisoning fish. The leguminous plant, *Piscidia*, of the West Indies, owes its name to this use of its bark. In the Dutch East Indies the cortex of the root of *Derris elliptica* and the seed of *Pachyrrhinus angulatus* are employed for this purpose. Both of these, according to Greshof,

contain a nonnitrogenous substance which is highly poisonous to fish, and relatively harmless to other animals. An extract of the derris root, which, in Borneo, is also used as an arrow poison, kills fish when mixed with water in the proportion of 1-25,000, and the active principle in a dilution of 1-5,000,000. Greshof has isolated both poisons and named them derrid and pachyrrhizid. A legumen, *Tephrosia ichthyonecea*, from West Africa, also yields a nonnitrogenous poison, but this affects other animals as well as fish. The fish poison of Java, from the seed of *Milletia atropurpurea*, contains saponin, and that of Ceylon, from *Hydrocarpus inebrians*, owes its effect to hydrocyanic acid. *Robinea nicon* of tropical America is used by savage tribes for the purpose of benumbing fish and this plant has been found to contain a white crystalline substance, freely soluble in alcohol, wholly insoluble in water. Water, to which an alcoholic solution of this poison has been added in the proportion of 1-1,000,000, kills fish. Other fish poisons of the West Indies are *Jacquinia armillaris*, which, on account of the fact that its dried fruit is used for bracelets, is now known as *bois bracelet*, and *Serjania letalis*, from which the poisonous honey of a certain wasp is prepared, the toxic action of which St. Hilaire has tested upon himself. This honey, even in small quantity, is said to produce a mild intoxication. This will remind the classical student of the poisonous honey connected with the retreat of the 10,000 Greek soldiers under Xenophon which occurred 400 years before our era. It will be understood, that so far we have discussed only those foods which are inherently poisonous.

The Spaniards use the word *siguatera* (pronounced sig-wah-té-ra) to designate the complex of symptoms induced in man by the eating of fish that are physiologically poisonous, and Blanchard has written as follows:

“*Siguatera* is an intoxication caused by fresh food, not infected by bacteria, and in which the poisonous principles are leukomains, formed by the physiologic activity of the tissues. I propose to designate this category of intoxication by the word *siguatera*, a name employed by the Spanish physicians of the Antilles to indicate poisoning by eating fish.”

In Russia many instances of fish poisoning are due to the fact that the fish are diseased and the disease is transmitted to man in his food. Instances of this kind of fish poisoning are well known in Germany also, and here they are generally due to eating diseased barbels. The symptoms are identical with those of cholera nostras and the disease is known as “barbencholera.” The poison, the nature of which is yet unknown, evidently reaches the mucous membrane of the stomach and intestines. This form of fish poisoning is sometimes called *ichthyotoxism gastricus*.

Schmidt concludes his studies on poisonous fish in Russia with the following statements:

“(1) Poisoning with fish is not due to putrefaction. (2) Fish poisoning (in Russia) is always due to some member of the sturgeon tribe. (3) The genesis of fish poisoning has no relation to the method of catching the fish, the use of salt, or imperfections in the method of preserving them. (4) The poisonous substance is not distributed throughout the animal, but is confined to certain parts. (5) The poisonous portion cannot be distinguished from the nonpoisonous, either macroscopically or microscopically. (6) The thoroughly cooked meat is never poisonous. (7) The fish poison is an animal alkaloid, produced most probably by bacteria that cause an infectious disease in the fish.”

Arustamow has studied 11 cases of fish poisoning in which five terminated fatally. In the fish, and in the liver, kidneys and spleen of the persons, bacteria, resembling, but not identical with, the typhoid bacillus, were found. The most noteworthy symptoms were general weakness, dull pain in the abdomen, dyspnea, mydriasis, vertigo, and dryness of the mouth. This author also concludes that the ill effects are due to bacteria which are pathogenic to the fish, and in the cases observed by him the meat was eaten raw.

Sieber found that the fish in an aquarium, from which some had been taken to supply a table and had proved poisonous, were sick and that as many as 30 died within the next two days. From the dead and sick fish Sieber obtained by anaerobic methods a highly toxicogenic germ, to which she gave the name *Bacillus piscicidus agilis*. This bacterium consists of highly motile, short rods, and old cultures show spore formations. The bacilli are easily colored with Ziehl's solution, and on gelatin and agar plates the colonies are granular, gray, or yellow. This organism liquefies gelatin and produces carbonic acid gas and small quantities of methylmercaptan. It is pathogenic to fish, mice, rats, frogs, dogs, and guinea pigs, and from the muscles of these animals the germ may be recovered in pure culture. After filtration through porcelain the sterilized cultures are quite as poisonous as before sterilization. Heat does not destroy the poison and at least one poisonous substance may be obtained by distillation. Filtered cultures give an intense red coloration with ferric chlorid. Sieber has obtained from growths of this bacillus, cadaverin and other known ptomains, but there are at least two undetermined bases present and one of these suffices to kill frogs in doses of 3.5 mg. The symptoms induced in animals by the use of sterilized cultures consist in shortness of breath and unrest, followed by apathy and paralysis.

Tyrotoxism.—In 1827 Hünnefeld made analyses of poisonous cheese and experimented with extracts upon the lower animals. He accepted the ideas of Kerner in regard to poisonous sausage in a somewhat modified form, and thought the active agents to be sebacic and caseic acids. About the same time Sertürner, making analyses of poisonous cheese for Westrumb, also traced the poisonous principles, as he supposed, to these

fatty acids. In 1848 Christison, after referring to the above mentioned work, made the following statement:

“His (Hünnefeld’s) experiments, however, are not quite conclusive of the fact that these fatty acids are really the poisonous principles, as he has not extended his experimental researches to the caseic and sebacic acids prepared in the ordinary way. His views will probably be altered and simplified if future experiments should confirm the late inquiries of Braconnot, who has stated that Proust’s caseic acid is a modification of acetic acid combined with an acrid oil.”

In 1852 Schlossberger made experiments with the pure fatty acids and demonstrated their freedom from poisonous properties. Since the overthrow of the fatty-acid theory, various conjectures have been made. In 1883 and 1884 there were reported to the Michigan State Board of Health about 300 cases of cheese poisoning. As a rule, the first symptoms appeared within from two to four hours after eating the cheese. In a few, the symptoms were delayed from eight to ten hours and in all these they were very slight. The attending physicians reported that the gravity of the symptoms varied with the amount of cheese eaten, but no one who ate of the poisonous cheese wholly escaped. One physician reported the symptoms as follows:

“Every one who ate of the cheese was taken with vomiting, at first of a thin, watery, later of a more consistent reddish-colored, substance. At the same time the patient suffered from diarrhea with watery stools. Some complained of pain in the region of the stomach. At first the tongue was white, but later it became red and dry; the pulse was feeble and irregular; countenance pale with marked cyanosis. One small boy, whose condition seemed very critical, was covered all over the body with bluish spots.”

Notwithstanding the severity of the symptoms in many, there was no fatal termination among these cases, though several deaths from cheese poisoning in other outbreaks have occurred. Many of the physicians at first diagnosed the cases from the symptoms as arsenical poisoning, and on this supposition many of them administered ferric hydrate. Others gave alcohol and treated upon the expectant plan. Vaughan, to whom the cheese was sent for analysis, made the following report:

“All of these 300 cases were caused by the eating of twelve different cheeses. Of these, nine were made at one factory and one each at three other factories. Of each of the twelve I received smaller or larger pieces. Of each of ten I received only small amounts. Of each of the other two I received about 18 kilograms. The cheese was in good condition, and there was nothing in the taste or odor to excite suspicion. However, from a freshly cut surface there exuded numerous drops of a slightly opalescent fluid which reddened litmus paper quickly and intensely. Although, as I have stated, I could discern nothing peculiar in the odor, if two samples, one of good, the other of poisonous cheese, were placed before a dog or cat, the animal would invariably select the good cheese; but if only poisonous cheese were offered and the animal was hungry, it would partake freely. A cat was kept for seven days and fed only poisonous cheese and water. It ate freely of the cheese and manifested no untoward symptoms. After the seven days the animal was etherized and abdominal section made. No abnormality

could be found. I predicted, however, in one of my first articles on poisonous cheese that the isolated poison would affect lower animals. At first I made an alcoholic extract of the cheese. After the alcohol was evaporated *in vacuo* at a low temperature a residue, consisting mainly of fatty acids, remained. I ate a small bit of this residue and found that it produced dryness of the throat, nausea, vomiting, and diarrhea. The most of this extract consisted of fats and fatty acids and for some weeks I endeavored to extract the poison from these fats, but all attempts were unsuccessful. I then made an aqueous extract of the cheese, filtered this, and drinking some of it, found that it also was poisonous. But after evaporating the aqueous extract to dryness on the water-bath at 100° the residue thus obtained was not poisonous. From this I ascertained that the poison was decomposed or volatilized at or below the boiling point of water. I then tried distillation at a low temperature, but by this the poison seemed to be decomposed. Finally, I made the clear, filtered aqueous extract, which was highly acid, alkaline with sodium hydrate, agitated this with ether, removed the ether and allowed it to evaporate spontaneously. The residue was highly poisonous. By re-solution in water and extraction with ether, the poison was separated from foreign substances. As the ether took up some water, this residue consisted of an aqueous solution of the poison. After this was allowed to stand for some hours *in vacuo* over sulphuric acid, the poison separated in needle-shaped crystals. From some samples, the poison crystallized from the first evaporation of the ether and without standing *in vacuo*. This happened only when the cheese contained a comparatively large amount of the poison. Ordinarily, the microscope was necessary to detect the crystalline shape. From 16 kilograms of one cheese I obtained about 0.5 gram of the poison, and in this case the individual crystals were plainly visible to the unaided eye. From the same amount of another cheese I obtained only about 0.1 gram, and the crystals in this case were not so large. I have no idea, however, that by the method used all the poison was separated from the cheese.”

To this substance the name tyrotoxinon (cheese poison), which had formerly been used to designate the undiscovered active agent in poisonous cheese, was given. In 1887 Wallace found tyrotoxinon in two samples of cheese which had caused serious illness. The first of these came from Jeanesville, Pa., and the symptoms as reported to Wallace by Doolittle, who had charge of the cases, were as follows: Some 50 persons were affected and in the majority of these the symptoms appeared within from two to four hours, and consisted of vertigo, vomiting, and severe rigors, varying in their order of appearance and severity. Chills and vomiting were the most constant and marked symptoms, and were soon followed by pain in the epigastric region, cramps in the feet and lower limbs, purging and griping pain in the bowels, a sensation of numbness, especially in the limbs, and marked prostration, in some amounting almost to collapse. The vomit at first consisted of the contents of the stomach and had a strong cheesy odor; afterward, it contained mucus, bile, and in the more severe cases, blood. The diarrheal discharges, at first fecal, later became watery and light colored. No deaths resulted, and for the most part the effects were transient, and all that remained on the following day were the prostration and numbness, which disappeared in from one to three days. Children apparently suffered less than adults.

All remarked on the suddenness of the attack, feeling perfectly well until nausea and vertigo set in.

Wolff detected tyrotoxin in cheese which poisoned several persons at Shamokin, Pa. The pores of this cheese were found filled with a grayish-green fungoid growth, though it is not supposed that this was connected in any way with the poisonous nature of the food. Tests were made for mineral and vegetable poisons with negative results, after which tyrotoxin was recognized both by chemical and physiologic tests.

Dokkum obtained from poisonous cheese, by a modification of the method already given for the separation of tyrotoxin, a basic substance, which when injected into frogs in doses of 5 mg. caused paralysis, and death within 30 minutes. This investigator concluded that the base thus obtained by himself is not a tyrotoxin but a curare-like poison, for which he suggested the name tyrotoxin.

Tyrotoxin has been found in milk in numerous instances, having first been detected in this fluid in 1885, soon after its discovery in cheese. In 1886 Newton and Wallace detected this poison in milk which seriously affected a large number of persons at Long Branch, N. J. The poisonous milk came solely from one dairyman and investigation showed the following condition of affairs: The cows were milked at the unusual hours of midnight and noon, and the noon's milk—that which alone was followed by illness—was placed while warm in the cans, and then, without any attempt at cooling, carted eight miles during the warmest part of the day in a very hot month. During this time the unknown germ which elaborates tyrotoxin undoubtedly grew abundantly in the milk and its toxin was easily detected both by chemical and physiologic tests. In the same year Scheerer found tyrotoxin in milk used by, and in the vomited matter of, persons made sick at a hotel at Corning, Ia. In 1887 Firth, an English army surgeon, stationed in India, reported an outbreak of milk poisoning among the soldiers of his garrison. From the milk, he separated, by the method already given, tyrotoxin and demonstrated its action upon the lower animals. In the same year Vaughan reported the Milan cases of milk poisoning, three of which terminated fatally. His report of his observation of the symptoms is as follows: I first saw these patients, Sunday, September 25; on a sofa in the room we found the daughter, who had been vomiting during the day and seemed much exhausted. She was not inclined to talk, and seemed to be in a stupor, though when spoken to she responded rationally. Her pupils were slightly dilated, her tongue coated, her pulse 120 and weak; her face pale; and a violent throbbing could be felt over the abdomen, which was retracted. Her temperature was 96°. In another room were the father, mother, and son, two of them dying. The father was rational and talked with some freedom, when asked concerning the kind of food they had

been eating. His pupils were normal, his face could not be said to present any peculiar feature, his pulse was rapid, breathing somewhat rapid, and the throbbing in the abdominal area was plainly felt. The abdomen was retracted and there was no pain on pressure. He complained of a burning constriction of the throat, swallowed with difficulty, and said that his throat and stomach felt as though they were on fire. The mother lay with eyelids closed as if in a deep sleep. Her pulse was rapid, her face had a livid flush, her breathing was about 35 per minute, and labored. The skin was cool, but neither abnormally moist nor especially dry and harsh. She could not be aroused; in fact, she was comatose. The son rolled uneasily from one side of the bed to the other. His breathing also was labored. His eyelids were closed, and the pupils were markedly dilated—did not respond to light. He could not be aroused. In mother and son, as well as in father and daughter, the abdomen was retracted, and the throbbing in the abdominal area was easily felt. The symptoms were not those of morphin, strychnin, digitalis, or aconite. They did have some resemblance to those of belladonna, but were not identical; the pupils were not so widely dilated as they are in belladonna poisoning; there was in none of these persons the active delirium of belladonna poisoning; there was no picking at the clothing; no grasping of imaginary objects in the air; no hallucinations of vision.

An autopsy on one of the fatal cases showed as the most marked abnormality, tightly constricted areas of the large intestine such as is sometimes seen in lead poisoning, and which had been quite generally observed in the lower animals experimentally killed by the administration of tyrotoxin. Novy tested a cold-water extract of the finely divided intestines for poisons. The fluid, which was acid in reaction, was filtered, then neutralized with sodium carbonate and shaken with ether. The ether, after separation, was removed and allowed to evaporate spontaneously. The residue was dissolved in water and extracted again with ether. This ether residue gave the chemical reaction for tyrotoxin and a portion of it was administered to a kitten about two months old. Within one-half hour the kitten began to retch and soon it vomited, and within the next three hours it vomited five times. There was no purging, but the retching and heavy breathing, with evidences of prostration, continued more or less marked for two days, after which the animal slowly recovered.

Samples of fresh milk were inoculated with some of the vomited matter, with the contents of the stomach, with an aqueous extract of the intestine, and with a small portion of the soil which had been taken from the floor of the buttery. Tyrotoxin was obtained from all of these after they had been kept at from 25° to 30° for 24 hours.

In 1899 there was an outbreak of cheese poisoning at Aldershot, Eng-

land, in which 27 individuals were involved, and three deaths resulted. The chief symptoms were vomiting, feeble pulse, cramping in the legs, followed by jaundice, and accompanied by a temperature which varied from 100° to 103°. Of 20 sheep fed upon the camp refuse, including potato peelings, onions, pieces of cheese, etc., eight sickened and two died within from two to three days. After burial three of these sheep were exhumed. From a piece of cheese obtained in the stomach of one of these animals, Luff found tyrotoxicon in fairly large quantity and one milligram of this injected into a rat killed it in three hours. In an outbreak in London, one analyst, examining the cheese, reported that he obtained a small amount of a body possessing the chief characteristics of tyrotoxicon, but this he obtained from only two out of four samples and then in small quantity only. Two other chemists, examining samples of this cheese, failed to find this poison. In 1898 Wesener and Rossmann isolated tyrotoxicon from poisonous cheese in crystalline form. LePierre obtained a basic body having the formula, $C_{16}H_{23}N_2O_4$, from poisonous cheese.

Kinnicutt, at that time professor of chemistry in the Polytechnic School at Worcester, Mass., extracted tyrotoxicon from milk which had been kept for some hours in unclean vessels.

During the eighties of the nineteenth century when cheese poisoning was so frequent in Michigan and in other parts of the United States, it happened frequently that similar symptoms resulted from the eating of ice-cream, frozen custard, cream puffs, and other articles of food consisting largely of milk. At first the injurious effects of these substances were attributed to plants eaten by the animals and to the flavoring and coloring matters used in the preparation of these foods. Even within more recent years, the claim has been put forward that ice-cream poisoning is due to artificially prepared vanillin, but vanilla extracts used in the preparation of foods, which proved to be poisonous, have been swallowed in large quantities by chemists and have been administered to animals without the slightest result. It has also been claimed that ice-cream often owes its poisonous properties to small quantities of zinc or tin dissolved during the process of freezing. This statement is absurd when we find, as we frequently did, that a sample of ice-cream will act more powerfully as an emetic than will sulphate of zinc, grain for grain. It is within the range of possibility that poisonous extracts may be used in flavoring milk preparations and it is a well-known fact that chromate of lead has been found in cream puffs. But it is certainly true that neither flavoring agent nor metals is accountable for the injurious effects observed to follow the eating of poisonous ice-cream and similar milk products. Moreover, ice-cream flavored with chocolate and that flavored with lemon also have been found to be poisonous, and vanilla ice-cream was at that time more

frequently poisonous for the very good reason that this flavoring was used more largely than all others combined.

Vaughan and Novy found tyrotoxicon in numerous samples of poisonous ice-cream and custard. Schearer reported the same poison in both vanilla and lemon ice-cream which made many sick at Nugent, Ia. Allaben observed numerous cases poisoned with lemon ice-cream, and Wellford obtained tyrotoxicon from custard flavored with lemon. While tyrotoxicon was found in milk, cheese and other milk products, frequently during the eighties in this country, more rarely in England, and at least once in India, since 1890, it has not so far as we know, been found in this country in any form of food poisoning. Vaughan was the first to recognize this fact. In 1890, in numerous samples of poisonous cheese, he failed to find any evidence of tyrotoxicon. From some of these cheeses he obtained an albumose, 40 drops of an aqueous solution of which when injected under the skin of the backs of cats produced vomiting and purging, followed by marked prostration and terminating in some instances in death. In 1895 Vaughan and Perkins obtained from a piece of cheese which had proved fatal to one man, two bacilli, one of which elaborated an active poison; both filtered and heated cultures killed animals promptly. On account of a mistaken label, 10 drops of a filtered culture from one of these organisms was injected subcutaneously into a man. Vomiting, purging, and collapse, ending, however, in recovery, followed. Vaughan and McClymonds examined 65 samples of cheese from as many different manufacturers. Of these, 49 were what is ordinarily known as American green cheese. They were made in Michigan, Wisconsin, Illinois, New York, and Canada. Eight of the 49 samples were sent to the laboratory because persons eating them had suffered from nausea, vomiting, and purging; the other samples were not known to have had any deleterious effects. Every one of the 49 samples of American green cheese furnished cultures which killed white rats, guinea pigs, and rabbits. The toxicogenic bacterium in all these samples was found to belong to the colon group and whether or not a given sample of green cheese unpleasantly affects the consumer will depend upon the amount and virulence of the germ present in the cheese.

It may be said that in the eighties of the last century when poisoning with milk and its products was so common, there was no adequate sanitary supervision of milk or milk supplies in this country. The farmers for miles roundabout cheese factories carted their dirty milk to the factory where it was all dumped into the vats. The bacterial flora of every barnyard in the district contributed its widely varied products to the cheese manufacturer. There was no such thing as dairy inspection. There was no attention given to the cleanliness of the udders of the cows or the hands of the milkers. There was no attention paid to the possi-

bility of infection which might result from the use of dirty pails. No doubt polluted water was in some instances added as a diluent to the milk. No one dreamed of chilling the milk after it was drawn and it stood for hours in the farmer's barnyard and rested for other periods of time in his cart as he drove to the cheese factory, at a temperature most favorable for the growth and multiplication of the innumerable and variegated bacteria which it might contain. In part as a result of these researches, dairies were submitted to inspection. The health conditions of cows were investigated. A certain standard for stabling was demanded. The udders were cleaned before milking. The milkmaid or boy was advised to wash her or his hands before operating. Provision was made for lowering the temperature of the milk soon after it was drawn. Ice tanks were provided for its transportation and finally came sterilization and pasteurization. During the eighties and early nineties of the last century one or more bacteriologists and chemists were kept busy in the Hygienic Laboratory of the University of Michigan examining cheese and other milk products. During the nineties the number of samples sent in rapidly decreased and in the past 20 years only one sample of poisonous cheese has found its way to this laboratory. It is quite safe to state that in most instances of poisoning with milk and its products the poisonous principles are the products of the bacteria which are present in the food, and quite naturally, chemical poisons are as varied as are the microorganisms which elaborate them. We are now fairly competent to handle milk and its products in such a way that bacteria will not have opportunity to employ them as culture media in which to grow and elaborate their poisons. This is not the place to give facts concerning milk and its products as agents in the dissemination of infections. A discussion of this subject belongs to the sections devoted to the several diseases which may be transmitted through these foods.

The chemistry of tyrotoxicon remains unknown. At one time Vaughan, on insufficient evidence, believed it to belong to the diazo group. It is certain that the cheese poisoning of former times was not botulism. As we shall show in the next chapter, a clear distinction between "cheese poisoning" and "sausage poisoning" was drawn about one hundred years ago. This does not mean that botulism is never due to cheese, or that other foods may not at times be poisonous without bearing *B. botulinus*.

Mytilotoxism.—Literally this heading includes only poisoning with mussels, but for convenience we shall include all instances of poisoning with shell fish of any kind. Judging from the symptoms induced, there are three kinds of poisonous mussel. In some instances the symptoms resemble those induced by a gastrointestinal irritant. Fodéré reports the case of a soldier, who, after eating a large dish of mussels, suffered

from nausea, vomiting, pain in the stomach, tenesmus, and rapid pulse. After death, which occurred within two days, the stomach and intestines were found inflamed and filled with tenacious mucus. Combe and others have also reported cases of the choleraic form of mussel poisoning.

The symptoms, however, most frequent in man after the eating of poisonous mussels are more purely nervous. A sensation of heat and itching appears, usually in the eyelids, soon involving the whole face, and perhaps a large portion of the body. An eruption, usually called nettle-rash, though it may be papular or vesicular, covers the parts. The itching is most annoying, and may be accompanied by marked swelling. Often there is asthmatic breathing, which is relieved only by ether. In some cases reported by Mohring, dyspnea preceded the eruption, the patients became insensible, the face livid, and convulsive movements of the extremities were noticed. Burrows reports similar cases, with convulsive tremors, coma, and death within three days. This in condensed form is a statement of the older reports concerning poisoning with mussels, clams, and similar articles of diet. We have seen several cases of this variety of mytilotoxism and have had opportunity not only to observe it, but to a certain extent to experiment with those susceptible to it. Such cases are unquestionably instances of food sensitization. It occurs in those who have been sensitized to this form of food and is induced among these individuals on eating very small amounts of the special food to which they have been sensitized. We have had opportunity to study one case sensitized to clams only. This individual can eat oysters, crabs, lobsters, and all ordinary shell fish with the exception of clams, without any untoward effect, but the smallest flavor of a clam in a broth will produce in a slight and transient way the symptoms mentioned above, while larger amounts will be followed by most alarming symptoms.

In a third class of cases there may be observed intoxication resembling that of alcohol, followed by paralysis, coma, and death. In 1827 Combe observed 30 persons poisoned, two of them fatally, with mussels. The symptoms were as follows:

"None, so far as I know, complained of anything peculiar in the smell or taste of the animals and none suffered immediately after taking them. In general, an hour or two elapsed, sometimes more; and the bad effects consisted rather in uneasy feelings and in debility than in any distress referable to the stomach. Some children suffered from eating only two or three; and it will be remembered that Robertson, a young and healthy man, only took five or six. In two or three hours they complained of a slight tension of the stomach. One or two had cardialgia, nausea, and vomiting; but these were not general or lasting symptoms. They then complained of a prickly feeling in their hands, feet, and constriction of the mouth and throat, difficulty of swallowing, and speaking freely, numbness about the mouth, gradually extending to the arms, with great debility of the limbs. The degree of muscular debility varied a good deal, but was an invariable symptom. In some it merely prevented them from walking firmly,

but in the most of them it amounted to perfect inability to stand. While in bed they could move their limbs with tolerable freedom, but on being raised to the perpendicular posture they felt their limbs sink under them. Some complained of a bad, coppery taste in their mouths, but in general this was in answer to what lawyers call a 'leading question.' There was slight pain in the abdomen which increased on pressure, particularly in the region of the bladder, which organ suffered variously in its functions. In some the secretion of urine was suspended, in others it was free, but passed with pain and great effort. The action of the heart was feeble; the breathing, unaffected; the face pale, expressive of much anxiety; the surface, rather cold; the mental faculties unimpaired. Unluckily, the two fatal cases were not seen by any medical person, and we are, therefore, unable to state minutely the train of symptoms. We ascertained that the woman, in whose house were five sufferers, went away as in a gentle sleep, and that a few minutes before death she had spoken and swallowed."

The woman mentioned by Combe died within three hours and the other death was that of a watchman, who was found dead in his box, six or seven hours after he had eaten of the mussels. Postmortem examination of these showed no abnormality; the stomach contained some of the food partially digested. The explorer, Vancouver, reports four cases similar to those observed by Combe. One of the sailors died in five and one-half hours after eating the mussels.

Schmidtman reported cases observed by himself in workmen and members of their families who had partaken of mussels taken near a newly constructed dock, the symptoms appearing according to the amount eaten, from soon after eating to several hours later. There was a sensation of constriction in the mouth, throat, and lips. The teeth were set on edge as though sour apples had been eaten. There was no headache; a sensation of flying, and an intoxication similar to that produced by alcohol. The pulse was hard and rapid; no elevation of temperature; the pupils were dilated and reactionless. Speech was difficult, broken, and jerky. The limbs felt heavy; the patients grasped spasmodically at objects and missed their aim. The legs were no longer able to support the body. The knees knocked together. There was nausea, vomiting, no abdominal pain, no diarrhea. The hands began to feel cold. The sensation of cold soon extended over the entire body, and in some the perspiration flowed freely. There was a feeling of suffocation, often a restful and dreamless sleep. One person died in one and three-quarters hours, another in three and one-half hours, and a third in five hours, after eating of the mussels. In one of these fatal cases, rigor mortis was marked and remained for 24 hours. The vessels of all the organs were distended, only the heart was empty. There was marked hyperemia and swelling of the mucous membrane of the stomach and intestines, the spleen was enormously enlarged, and the liver showed numerous hemorrhagic infarctions.

Many theories have been advanced to account for poisonous mussels. It was formerly believed that the effects were due to the copper which the animals obtained from the bottoms of vessels, but, as Christison re-

marks, copper does not produce these symptoms. Moreover, Christison made analyses of the mussels which produced the symptoms observed by Combe, and was unable to detect any copper. Bouchardat found copper in some poisonous mussels, but he does not state the amount of metal or the source of the animals. Edwards advanced the theory that the symptoms were wholly due to idiosyncrasy of the consumer. This certainly is not a tenable hypothesis in such instances as those reported by Combe and Schmidtman, where a large number of those who partook of the food were affected. Coldstream stated that the livers of poisonous mussels are larger, darker, and more brittle than the normal, and these changes he believes are due to a diseased condition of the animals. Many have supposed that the poisonous effects were due to a peculiar species of medusa upon which the mussels fed, and De Baume found in the vomited matter of one person some medusae. He states that these are most abundant during the summer when the mussels are most frequently found to be poisonous. The theory of Burrows that mussels are always poisonous during the period of reproduction, at one time received considerable credit. However, cases of poisoning have occurred at different seasons of the year. In 1872 Crumpe suggested that there is a species of mussel which is in and of itself poisonous, and this species is often mixed with the edible variety. It has been stated that the poisonous species has a brighter shell, a sweet, more penetrating, bouillon-like odor, than the nonpoisonous; also that the flesh of the former is yellow and that the water in which they are cooked is bluish. This theory, however, is opposed by the majority of zoölogists. Möbius states that the peculiarities of the supposedly poisonous variety pointed out by Virchow and Schmidtman are really due to the conditions under which the animals live, the amount of salt in the water, the temperature of the water, whether it is moving or still water, the nature of the bottom, etc. He also states that the sexual glands which form the greater part of the mantle, are white in the male and yellow in the female. The theory of a poisonous species has been abandoned since it has been shown that edible mussels may become poisonous if left in filthy water 14 days or longer, and, on the other hand, poisonous ones may become fit for food if kept for four weeks in good water.

Cats and dogs which have eaten voluntarily of poisonous mussels have suffered from symptoms similar to those observed in man; and rabbits have been poisoned by the administration of the water in which the food has been cooked. A rabbit treated in this manner by Schmidtman died within one minute. From these mussels Brieger extracted the ptomain, mytilotoxin. Whether those mussels which produce other symptoms also contain similar poisons remains for further investigations to determine.

In 1887, three cases of mussel poisoning, one fatal, occurred at Wilhelmshaven, the place which supplied Brieger with the mussels from which he obtained mytilotoxin. Schmidtman found that nonpoisonous mussels placed in the water of this bay soon became poisonous, and that the poisonous mussels from the bay placed in the open sea soon lose their poisonous properties. Linder has found in the water of this bay and in the mussels living in it a great variety of protozoa, amoebae, bacteria, and other organisms which are not found in the water of the open sea, nor in the nonpoisonous mussels. He also ascertained that if the water of the bay be filtered, nonpoisonous mussels placed in it do not become poisonous, and he concludes that poisonous mussels are those which are suffering from disease due to residence in filthy water. Cameron makes a somewhat similar statement about the poisonous mussels near Dublin, taken from water contaminated with sewage. He found that the livers of these animals were much enlarged and from them he obtained a base that is probably identical with mytilotoxin. That oysters taken from beds near the outlets of sewers may be contaminated with the specific germ of typhoid fever has been well demonstrated within the past few years, and that they may become poisonous in the same way that mussels acquire harmful properties is also well known. Pasquier reported cases of poisoning at Havre from the eating of oysters taken from an artificial bed near the outlet of a drain from a public water-closet. Christison says that an unusual prevalence of colic, diarrhea, and cholera at Dunkirk was believed to have been traced to an importation of oysters from the Normandy Coast. There should be police regulation against the sale of all kinds of mollusks and all kinds of fish as well, taken from filthy water. Special attention should be given to localities that have once supplied poisonous food of this kind. Many popular rules have been formulated for the easy recognition of poisonous mussels, and to some of these credence has been given by medical authors. An unusually large mussel is regarded with suspicion, and Lohmeyer gives measurements that may guide the individual in search of this article of food. Stress is placed on color by some, and one is advised to avoid the dark brown-blue and purchase the dark-blue or dark green-blue. We may expect to see the prudent, hungry man draw from his pocket a scale of colors and carefully compare it with the shell of the juicy bivalve before he consigns it to his digestive organs, if he is to observe the rules laid down in some recent medical works. Then he will take the dimensions of the whole, measure the thickness of its shell, then its strength, for we are informed that the poisonous clam has a thin, brittle shell. Seriously, one is to avoid shell fish from impure water and he may properly insist that they be washed in clean water, and certainly one should avoid eating this kind of food

when it had stood for a few hours at summer heat in the form of broth. A few years ago the U. S. Public Health Service made a study of the oyster beds in the Lower Potomac River and they found the oyster fishermen by the hundreds passing most of their time in dredging for oysters in shallow water and at the same time depositing their excreta into the water from which they took these bivalves. Under such conditions it was unnecessary to go back up the river many miles to study the effect of the sewage of Washington on the oyster beds in the Lower Potomac and in Chesapeake Bay.

Kreotoxism.—It has long been known that the flesh of animals dead from certain diseases or slaughtered while suffering from these diseases is not safe food for man. The Mosaic law forbade the eating of the flesh of animals dead from disease.

“Ye shall not eat of anything that dieth of itself: thou shalt give it unto the stranger that is in thy gates, that he may eat it; or thou mayest sell it unto an alien: for thou art an holy people unto the Lord thy God. Thou shalt not seethe a kid in his mother’s milk.” (Deut. 14:21).

The first part of this command is certainly wise counsel, but the feeding of a visitor with such food would not now be regarded as in accord with the rules of hospitable entertainment, and the sale of it even to an alien should not be permitted by the law of any country. The most common diseases that may be transmitted from the lower animals to man by the consumption of the flesh or milk of the former as food by the latter, are tuberculosis, anthrax, symptomatic anthrax, paratyphoid fever, puerperal fever, pleuropneumonia, glanders, various septicemias, trichinosis, mucous diarrhea, and actinomyces. We are, however, not just now discussing the transmission of infectious diseases from the lower animals to man, but are devoting our attention to the untoward effects which arise from the eating of poisonous flesh, whether the animal which furnished it was at the time of slaughter specifically infected or not.

In meat which had poisoned a large number of persons, Gaertner found his *Bacillus enteritidis*. The meat was from a cow that had a severe diarrhea for two days before she was killed. Of the twelve persons who ate of the flesh raw, all became sick; while of those who ate of the cooked food, a large percentage were also affected. In the meat, and in the spleen of a person who died, Gaertner found a bacillus which proved fatal to animals. Good beef, inoculated with this bacterium and kept for some hours, killed rabbits, guinea pigs and mice. The skin of the people who were poisoned and recovered peeled off. The period of incubation varied from two to thirty hours. Even the boiled bouillon cultures of this bacillus are highly poisonous, showing that the poisonous properties are not destroyed by cooking the meat. Fischer reports the following: A cow, that had recently calved, had been sick for some eight

days, and on account of this illness she was killed. The animal was slaughtered on Friday and on the following Sunday at noon 19 persons ate of the meat. The prominent symptoms were vomiting and violent purging, appearing a few hours after the meal. Vertigo, loss of consciousness, and exfoliation of the epidermis during recovery, all of which were observed by Gaertner in some of his cases, were not present in any case reported by Fischer. Notwithstanding these differences, a study of the bacillus led to the conclusion that it is identical with the *Bacillus enteritidis*. By concentrating a filtered culture and precipitating the filtrate with absolute alcohol the crude poison was obtained. It gave the general reactions for peptons, and boiling for an hour and a half did not perceptibly weaken its poisonous properties. Lubarsch reported the death of a child two days old from septic pneumonia caused by the *Bacillus enteritidis*. Section showed pleuritis and pneumonia of the left lower lobe, bilateral purulent bronchitis, atelectasis of the right lung, parenchymatous cloudiness of the kidneys, fatty infiltration and engorgement of the liver, slightly enlarged spleen, uric acid infarction of the kidneys, and icterus neonatorum. All other pathologic conditions were supposed to be consequent upon the septic pneumonia. White rats and chickens proved to be wholly immune, while guinea pigs, rabbits, and mice were susceptible to the bacillus found in the tissues of the child. These susceptible animals were killed within from 16 to 24 hours by intraperitoneal inoculations and in from two to four days by subcutaneous injections. In all cases, section showed marked congestion of the intestines, swelling of the follicles, and in some instances slight erosions of the mucous membrane. After intraperitoneal inoculation, serofibrinous or hemorrhagic peritonitis developed. After subcutaneous inoculation in rabbits, sometimes in guinea pigs, there was a serofibrinous pleuritis, with compression of the lungs and in one instance a circumscribed pneumonia. Sterilized cultures in large quantities produced the same effect as the unsterilized. The symptoms and anatomic changes induced by this bacterium agree with those observed in Winkel's disease, in the rapidly fatal progress, cyanosis, icterus, rapid respiration, tendency to hemorrhage, and fatty degeneration. The most essential difference lies in the fact that hemoglobinuria is a prominent symptom of Winkel's disease, while it does not occur after inoculation with the *Bacillus enteritidis*. In August, 1887, 256 soldiers and 36 citizens at Middleburg, Holland, were taken sick after eating meat from a cow which had been killed while suffering from puerperal fever. The symptoms were nausea, purging, elevation of temperature, and prostration. In some, there were observed dizziness, sleeplessness, and dilation of the pupil. After a few days these symptoms gradually disappeared, and in many an eczematous eruption of the lips gave annoyance. Pigs, cats,

and dogs that ate of the offal of this animal were also made sick. Thorough cooking did not destroy the poison, and those who took soup and bouillon made from the meat were affected like those who ate of the muscle fiber. In most of the cases the symptoms came on within 12 hours after eating the meat.

Basenau first found his *Bacillus bovis morificans* in the flesh of a cow that was killed while suffering from puerperal fever, and later he has detected the same microorganism in the meat of animals killed while sick with perforative peritonitis, puerperal paralysis, and chronic pyæmia. It seems from the researches of this investigator that there are varieties of this bacillus, the poisons of some of which are destroyed by heating to 100°, while those of others are not. It is more than probable that Basenau's bacillus is a variety or a strain of *Bacillus enteritidis* and that the poison is contained within the bacterial cell, and whether or not meat infected with this organism will prove harmful depends upon the number of bacteria present.

In 1894 Vaughan and Perkins examined some dried beef which had seriously poisoned a family of four. There was nothing in the appearance or odor of this beef to cause any suspicion; in fact, it seemed to be of exceptionally good quality. Anaerobic cultures from the interior of the meat were made and developed a bacillus, from two to three times as long as broad, taking the ordinary stains, motile, with no spore formation, not liquefying gelatin, but coagulating milk, growing best at the temperature of the body, but developing its poison at ordinary temperature, producing gas abundantly, and pathogenic to white rats, rabbits, and guinea pigs. Sterilized cultures were also poisonous.

Of 200 men at a banquet at Sturgis, Mich., in April, 1894, every one who ate of the pressed chicken served was made ill. Some who were not at the banquet, but who aided in preparing it, took small bits of the chicken, and these also were made sick. All were taken within from two to four hours after eating the chicken, with nausea, violent griping, and purging; many fainted while attempting to rise from bed. The chickens were killed Tuesday afternoon, picked and left hanging in the market room (not in a cooling room) until Wednesday forenoon, when they were drawn and carried to a restaurant and here left in a warm room until Thursday morning, when they were cooked (not very thoroughly), pressed and served at the banquet that night. This food was examined by Vaughan and Perkins, and found to contain two microorganisms, a slender bacillus from four to five times as long as broad, and a streptococcus. The bacillus was fatal to white rats, guinea pigs, and rabbits, when administered intraperitoneally, intravenously, and subcutaneously. The streptococcus was not fatal when given in pure cultures, but mixed cultures of the two induced death; and in these

instances when administered subcutaneously, in addition to lesions found after the employment of pure cultures of the bacillus, there was extensive sloughing. This bacillus is motile, takes the ordinary stains readily, and is decolorized by Gram's method. It grows very slowly at ordinary temperature and rapidly at 37°. Of two cultures of equal age, one grown at ordinary temperature and the other at 37°, 1 c.c. of the former was necessary to induce death, while $\frac{1}{4}$ c.c. of the latter proved fatal. The anaerobic cultures were more active than the aerobic, $\frac{1}{2}$ c.c. of a beef tea culture heated to 60° for thirty minutes proved fatal, while 1 c.c. heated to 100° for 15 minutes failed to kill.

In an outbreak of bromatotoxism at an asylum in Norway, the patients' food was veal, and in this Holst found a small bacillus similar to, but not identical with, that of Gaertner. Lewis found a ptomain which he supposed to be neuridin, in corned beef that poisoned people in Ohio. Poels reported cases of poisoning in Rotterdam from the eating of meat supposed to be from a healthy animal. A strain of the colon bacillus was found in this meat and it was shown that sterilized cultures were sufficiently active to kill calves. The same bacillus has been found in other outbreaks of kreotoxism in Holland. Zorkendorfer reported the presence of anthrax bacilli in some meat that poisoned many people, some fatally, near Teplitz in 1894. However, his identification of this organism cannot be regarded as positive. Di Mattei has stated that the flesh of animals dead from symptomatic anthrax may retain its power of infection after having been preserved in a dried state for ten years. Siedler reported four cases of poisoning from decomposed goose grease. The symptoms consisted of giddiness, prostration, and violent vomiting. Christison reported cases in which persons were seriously, some fatally, affected by eating various kinds of meat which had undergone partial putrefaction. Olliver found six persons poisoned, four of them fatally, by eating decomposed mutton, and he mentions similar cases due to eating ham. Boutigmy, having failed to find any poison in the meat furnished at a festival, and to which the serious illness of many was attributed, made a meal of stuffed turkey furnished by the same dealer, but after a short time his countenance became livid, his pulse small and feeble, a cold sweat bathed his body, and violent vomiting and purging followed. Geiseler observed nausea, vomiting, purging, and delirium after eating bacon which was imperfectly cured. Schröder reported cases of poisoning which were due to the eating of the flesh of an animal killed while suffering from foot and mouth disease. However, both bacteriologic and chemical investigations led to no results. Hermann and Kaensche found in some meat which poisoned people at Breslau, a typhoid-like bacillus whose poison is not destroyed by boiling. Kuborn found a piece of poisoned meat which was infected with *Staphylococcus*

pyogenes flavus. Johnne reported cases of sausage poisoning in which microorganisms similar to the *Bacillus enteritidis* were found.

Some writers on food poisoning would make *Bacillus enteritidis* the most frequent factor in the elaboration of the poisons which cause untoward symptoms as the result of eating certain foods. Whether this is justified or not depends upon what strains of bacilli are included in the *enteritidis* group. It is undoubtedly true that most cases of food poisoning in adults are due to bacteria which in their morphology and cultural characteristics lie between the colon bacillus and the typhoid bacillus. In this group there are included, among others, (1) some unusually virulent strains of the colon bacillus; (2) paratyphoid bacilli, especially *B. paratyphosus* B; (3) *Bacillus suipestifer*; (4) *Bacillus enteritidis*. Of each of these there are many strains differing one from the other in some respect, as, for instance, in greater motility, in variable effects on the fermentative sugars, and in virulence. It will depend largely upon the bacteriologist who is examining the harmful food as to where in this broad group he will locate the organism which he finds. All these strains have been found at one time or another in diseased men or animals apart from any consideration of food poisoning. While members of this extensive group are not constantly present in the excreta of perfectly healthy men and animals, there are among the healthy many carriers, and it is therefore not essential in order that the food may be poisonous that it come from a diseased animal or be handled by a diseased individual. Individual strains of this group differ in the readiness with which they produce poisons and in the intensity of the poison which they do produce. The rapidity of their growth is determined, among other things, by temperature. As we have already stated, it was shown by Vaughan and Perkins in 1894 that the organism with which they worked was in pure culture four times as poisonous when grown at 37° as when grown at ordinary room temperature, or about 24°. It follows from this that food infected with any of these organisms is more highly poisonous the higher the temperature, within limits, at which it is grown. It is, therefore, not surprising that there should be more instances of food poisoning in summer than in winter and more instances when the food has been kept at high temperature than when it has been kept at low temperature. From these facts we may conclude that it is wise to keep all food, especially all animal food, from the time of slaughtering to the time of its final preparation for serving, at relatively low temperatures. Savage, who has made a most valuable study of food poisoning in England, comes to the conclusion that the organism most frequently responsible for these outbreaks in England is the Gaertner bacillus. This certainly is true, not only in England, but so

far as we can judge, in this country, if one includes under the name Gaertner bacillus all the strains we have mentioned.

We prefer to designate the group of microorganisms which is so frequently responsible for outbreaks of food poisoning as the colon-typhoid group. The members of this group elaborate more or less active poisons under favorable conditions in certain foods.

The colon-typhoid group, with the most nonvirulent member of the colon group at the bottom and the most virulent typhoid bacillus at the top, includes a large number of varieties and strains of microorganisms with wide variations in their cultural and biologic properties. It is undoubtedly from the intermediate members of this broad group that many instances of food poisoning owe their origin. Many of these organisms are both toxicogenic and pathogenic. When we say that they are toxicogenic we do not mean that they produce toxins in the restricted and specific sense in which the word toxin is now used by scientific men. A toxin is a soluble extracellular substance which is destroyed at the temperature of boiling water and which when injected repeatedly, in nonfatal doses, into proper animals leads to the elaboration by the cells of that animal of an antitoxin. We will not say that no member of this group produces a toxin in this sense, but we do say that the production of a toxin in this sense in any large quantity by any of these organisms has never been satisfactorily and unquestionably demonstrated. Certain members of this group produce poisons, the exact nature of no one of which has as yet been determined. The chemistry of food poisoning is a complex and for the most part, as yet an unsolved problem. The weight of evidence at present is that at least some of the poisons produced by these organisms are not destroyed, at least not promptly, at the temperature of boiling water and no one of them has been shown, so far as we know, to produce in animals an antitoxin. These poisons are supposed to be partially digested proteins, or, as they have been called, split protein bodies. Whatever may be their chemical nature they must contain at least one poisonous group, but what the nature of this group is and what its chemical structure may be have not as yet been determined.

Some of these intermediate varieties and strains in the colon-typhoid group are highly infective to man and others only slightly so. It happens, therefore, in food poisoning that the effects may be limited to an intoxication which may be slight or severe, but in either case is only of moderate duration; while, on the other hand, there may be no immediate signs of intoxication but the individual may after days develop an infectious disease as a result of the food which he has eaten. A few years ago a social organization in Detroit chartered a boat and started on a pleasure trip to Lake Superior ports. On the second day out and while

in St. Mary's River, a duck dinner was furnished the passengers. During the following night and within from two to four hours after eating this dinner, many of the party suffered severely with gastrointestinal symptoms, nausea, vomiting, and purging, but these symptoms passed away within from 24 to 48 hours, while certain members of the party during the next two weeks developed fever and *B. paratyphosus B* was shown to be the infecting agent. Those who came down with typhoid fever were not limited to the group that suffered from the acute and immediate symptoms; in other words, in food poisoning of this kind, symptoms of intoxication may be the only evidence of anything wrong in the food, but others partaking of the dinner may subsequently suffer from an infection introduced into the body with the food. There is no necessary relation between the intensity of the intoxication and the certainty of infection. If in this instance there had been no one or no group of the party immediately affected, it is possible that the party may have dispersed and individuals may have subsequently developed typhoid fever without any suspicion that they had acquired the infection from a common source. In all cases of food poisoning there should be a careful bacteriologic examination of the food and if possible of the excretions from the body, and special attention in this bacteriologic examination should be given to search for members of the colon-typhoid group, especially to the identification of possible infecting bacteria. We quite agree with Savage that in many cases of food poisoning the offending organism belongs to the colon-typhoid group, or, as he prefers to call it, the Gaertner group.

There are numerous instances of infection with typhoid and paratyphoid through the food. One of the most interesting of these is that which occurred at Hanford, Calif., and was investigated by Sawyer. In this village there was a church dinner, served twice, at noon and in the evening. About 150 individuals participated in these two meals and 93 cases of typhoid fever resulted. Of the 150 who ate in the hall, 85 developed typhoid fever. The other cases were in families to which portions of the leavings of the table were carried. The food, which was abundant and varied, had been prepared in the several families interested in the church and had been brought to the building where parts of it were subjected to further cooking. Nine women were especially concerned in the preparation of the food in their homes and Sawyer very wisely directed his attention to these cooks, suspecting a typhoid carrier. Two of the nine were excluded as possible sources of infection, because their contributions were not served until the evening meal and they played no important rôle in the distribution of the food to the guests. Specimens of urine and feces were taken from the remaining seven cooks and sent to the State Board of Health Laboratory for investi-

gation. In the meantime, a study was made of the past experiences and family histories of these women. It was found that Mrs. X had been keeping a boarding-house in the village for many years and that from time to time during the past seven and a half years there had been cases of typhoid fever among her boarders, the origin of which the local health officials could not ascertain. The laboratory studies showed that Mrs. X was an abundant carrier of the typhoid bacillus. Just how long this woman had been distributing this bacillus no one could tell. So far as she knew she herself had never had the disease, but her daughter had suffered from it 35 years before and she had served the daughter as a nurse. It is possible that during all this time she had served as a culture flask for the growth of the typhoid bacillus. Although not entirely well during recent years, Mrs. X had manifested no symptoms which might attract attention to her intestines. She had no history of gall stones and had never suffered, at least markedly, from either prolonged constipation or severe diarrhea. Pure cultures were made from her feces and these were found to be agglutinated by the blood of the cases which had developed from the church dinner. In most instances this agglutination took place in high dilutions. There seemed, however, at first a marked improbability that the infection distributed at the dinner could have been due to Mrs. X. The one article of food which she had prepared was a large pan of Spanish spaghetti, and certainly if any dish served at the meal should be free from all possible infection, it would be well-baked spaghetti. She had prepared the spaghetti on the day before the dinner and it was brought to the church to be cooked only about one-half hour before the serving of the meal began. The dish of prepared spaghetti was put into the oven and the top soon became brown and crisp, and as it was needed for the table the portions were taken from the top. Sawyer prepared a dish of spaghetti, following in every detail the directions given him by Mrs. X. He had inoculated the ingredients of the dish with cultures of typhoid bacilli taken from the stools of Mrs. X. This experiment demonstrated that, although the temperature of the oven was between 160° and 170° C., the temperature just under the top of the food mass was only 54° C. and in the middle only 23° C. In another baking, the oven was kept at temperatures ranging between 207° and 214° C. After half an hour the pan was removed. The surface was dark brown and the bits of projecting spaghetti were more or less charred. The liquid around the margin was boiling vigorously and the contents of the dish were sizzling. The temperature just under the surface was 83° C., at the middle it was 28° C. and near the bottom, 48° C. Even after the dish had been kept in the oven for an hour the temperature in the middle was not above 42.5° C., a temperature by no means destructive to the typhoid bacillus. It is inter-

esting to note that those who ate of this meal and who afterwards developed typhoid fever scattered widely during the period of incubation. Two of the 93 persons developed the disease at San Francisco, 200 miles from Hanford, and other cases came down with it in widely separated villages and cities. Had this outbreak been studied by one less skilled in epidemiology, it is more than likely that the great majority of the cases, probably all, would have baffled every attempt to trace their origin. It is worthy of note that some of the people who participated in this dinner suffered that night from more or less intestinal disturbances, although Sawyer is inclined to the opinion that these early attacks of gastrointestinal nature were not caused by the food. The period of incubation in the majority of the cases in this epidemic proved to be shorter than the time usually regarded as the minimum. The first case developed three days after the meal. More cases showed their first definite symptoms six days after the infected food was eaten than on any other one day. One case, however, showed no signs of typhoid fever until the twenty-ninth day. This is an illustration of the frequently observed fact that certain individuals carry the typhoid bacillus, even in their bodies, and some in their blood, for a long time before the symptoms of the disease develop. It is an indication of that to which we have already had occasion to call attention—that in order to cause active disease a microorganism must be not only capable of living and multiplying in the human body, but there must be a reaction between the body cells and the invading cells. Why this reaction occurs early in some, late in others, and not at all in still others, is one of the most interesting of the many unsolved problems in epidemiology.

Paratyphoid fever frequently originates in infected food and *B. paratyphosus* B is generally the infecting agent. In these cases acute symptoms of gastrointestinal character manifest themselves in a much larger number of those infected and in a much more severe way than when infection is due to *B. typhosus*. It is not desirable that we should present any large collection of instances of this kind and we shall content ourselves with one illustration only. This concerns a report made by Bernstein and Fish. This outbreak occurred at Westerly, Conn., in July, 1915, and it originated from pies made in a certain restaurant. The pies were of varied composition and comprised cocoanut-custard, custard, squash, lemon, chocolate, berry, and apple. Those who ate of these articles of diet passed, for the most part, a relatively short period of incubation, or rather it was only a few hours before symptoms appeared. In some, symptoms were in evidence in four and one-half hours, but in the majority they were delayed from 12 to 19. Vomiting was a constant symptom and continued in many instances for six days. The vomited matter was green. There was marked diarrhea, associated with tenesmus.

The stools were of the consistency of pea soup, greenish, and giving off a highly disagreeable odor. The number of evacuations averaged from ten to twenty daily and the temperature rose in some instances to 103°. One child of eight years was in an unconscious state for two or three days and presented a marked rigidity of the neck, resembling that of cerebrospinal meningitis. In one there was suppression of urine. This case terminated fatally. There was marked mental depression and convalescence was protracted. Three died within four days after the appearance of the first symptoms and a fourth after three weeks of illness. The first fatal case was that of a man aged forty-nine in whom symptoms of marked severity came on seven hours after eating the pie and terminated fatally in 36 hours. Thorough chemical studies were made for inorganic poisons, with negative results. Bacteriologic cultures were made and by agglutination tests it was shown that the infecting organism was *B. typhosus* B. The serum of animals inoculated with the organism obtained from the pies and from the excretions of the patients agglutinated *B. typhosus* B in dilutions as high as 1-6,000, though usually in lower dilutions. This serum did not agglutinate at all cultures of *Bacillus enteritidis*.

There is another group which, according to some investigators, is at least an occasional cause of food poisoning. We refer to the proteus, the best known representative of which is generally designated as *B. proteus* or *proteus vulgaris*. Savage has made an excellent summary of cases of food poisoning attributed to this group of organisms; also of the experimental work which has been done with members of this group. We shall only briefly refer to some of the instances which Savage has assembled. In 1914 Metchnikoff fed to a young chimpanzee several tubes of *B. proteus* which he had isolated from the stools of an infant suffering from diarrhea. This animal developed a severe gastroenteritis and died after four days. A large number of *B. proteus* was found in the alimentary tract of the dead chimpanzee. The same investigator fed a broth culture of *B. proteus* mixed with the whites of egg to 37 nursing rabbits, 22 of which died after having suffered with the symptoms of cholera. Metchnikoff summed up his conclusions, resulting from this and similar experiments, as follows:

“The chief microorganism in the diarrhea of nurslings is *B. proteus*. Its presence is nearly constant in our cases of this disease, also its pathogenic rôle when administered by the mouth, either alone or associated with other microbes, demonstrates its preponderating importance.”

Some years ago Booker, after a long and patient study of infantile diarrhea, came to the conclusion that *proteus vulgaris* plays an important rôle, although it might not be the sole causal agent, in this disease. About the same time (1901-1904) Martin, studying the relation of proteus

vulgaris to diarrheal affections, extracted from the cellular substance of this organism a preparation which in moderate doses led to great lowering of body temperature in rabbits, accompanied by great weakness, violent intestinal evacuations, and in some instances these symptoms were followed by collapse and death. The poisonous substance studied by Martin was contained in filtered broth cultures and was not completely destroyed by heating, although its effect was weakened. Berthelot studied the intraperitoneal and intravenous effects of proteus vulgaris obtained from cases of infantile diarrhea on guinea pigs and rabbits. Such injections caused death in these animals, but it appears that this investigator made no experiment by feeding. It should be clearly understood that in all cases of food poisoning the effects of the bacilli found in the suspected food should be tested not only by subcutaneous, intraperitoneal, and intravenous injections, but also by feeding. After reviewing these and many other observations and experiments with the proteus, Savage concluded:

“From this summary of outbreaks it is evident that for none of them was it established that *B. proteus* was etiologically concerned.”

This conclusion may be justified, but in our opinion the possibility of a member of the proteus group being concerned in food poisoning should not be overlooked, and these organisms should be sought as well as those of the colon-typhoid group.

Savage is quite convinced that food poisoning should be considered a specific disease. If we interpret him correctly, he does not mean that there is only one microorganism which may render food harmful, but that all of the organisms which have this action on food belong to what he calls the Gaertner group. This investigator, who has done splendid work and who has had opportunity to investigate 112 outbreaks of food poisoning in England, concludes that putrefactive bacteria are never concerned in food poisoning. It will be well to know just what he means by putrefactive organisms, and, consequently, we quote his definition of putrefaction:

“By putrefaction is understood the decomposition of organic matter, chiefly protein in character, by the action of bacteria, by which it is split up into a number of chemical substances many of which are gaseous and foul-smelling.”

If Savage means that we are seldom poisoned by eating foods which are giving off gases and foul smells, we agree with him, because in the present state of civilization the majority of mankind are inclined to refuse to take such foods. Our English confrere, however, goes a little farther than we can possibly follow him. He thinks that there is no objection to eating food, even that which contains great masses of putrefactive microorganisms. In order that we may not misinterpret

him, we make the following additional quotation from his splendid monograph on food poisoning:

"In the first place massive bacterial infection with intestinal bacteria is exceedingly common and foods such as milk, ice-cream, brawn, and sausages are habitually consumed containing thousands of bacteria per cubic centimeter or gram, many of which are of direct intestinal origin. Food poisoning outbreaks should be of repeated and constant occurrence instead of being comparatively infrequent. Further, there should be a *special* incidence upon the types of food which are so frequently ingested loaded with excretal bacteria. Milk in particular should be always causing outbreaks, yet if Chapter V is consulted it will be noted that comparatively few outbreaks of definite food poisoning have been traced to milk, and nearly all were due to bacterial infection with a specific bacillus. If outbreaks are caused by massive nonspecific bacterial infection we would expect to get a definite relationship between dosage and the degree of infection. Those who ate little would have slight symptoms, those who ate 'not wisely but too well' would pay the heavier price, the children with their greater intestinal susceptibility would particularly be selected. There would also be, in the more widespread outbreaks, a tailing off of the severity of the symptoms where the infection was less massive. Nothing of this is the case, the relationship between dose and the severity of attack is at most very inconstant and frequently nonexistent, while there is no special incidence on children."

If Savage be right in this statement, we in this country have been all wrong in attempting to secure, especially for infantile feeding, milk which does not contain a great number of bacteria, we should have paid no attention to the number of bacteria in milk and should have confined our efforts to eliminating only those bacteria which belong to the Gaertner group; all our limitations on the number of bacteria that should be permitted in certified milk are worthless. Children, according to Savage, if we understand him correctly, would do just as well upon dirty milk as upon clean milk, provided the Gaertner group is excluded from both kinds. About 40 years ago some of us in this country came to the conclusion that all cases of summer diarrhea in infants, cholera infantum, and allied manifestations were due to food poisoning, and we set to work to secure for our little patients clean milk. In doing so we went to a lot of trouble. We demanded that dairies should be inspected; that the milkman should wash his hands before drawing the lacteal fluid; that it should be received into clean receptacles only, so constructed as to exclude dust and hairs that might fall from the cow; that the milk should, soon after being drawn, be reduced to a low temperature in order to inhibit the rapid growth of the bacteria; that it should be transported in iced cans, and that the number of bacteria per c.c. should be considered an index of the fitness of the milk as a food. In all of these precautions have we been in error? Does it make no difference how many bacteria there are in milk, provided there are none belonging to the specific group?

It is true that milk and its products do not play so large a part as some

other foods might, for instance, in outbreaks of food poisoning among adults, including older children. We have accounted for this, in part at least, by what we believe to be a fact—that in most meals from which food poisoning arises, milk plays but a small part so far as bulk is concerned, except in ice-cream, milk itself, cheese, and other special milk products. Moreover, in most dinners from which food poisoning arises the small amount of milk that is employed has been cooked. As we have already stated, we believe that the summer diarrheas of infancy are cases of food poisoning and that the poisonous food is milk—milk rendered poisonous either by a large number of ordinary, nonspecific bacteria, or possibly in a few instances milk contaminated by members of what Savage calls the Gaertner group. We dare say that the milk problem, so far as infant feeding is concerned, is a much more serious question in the United States than it is in England, and we have supposed this is due to the fact that in the summer season the average temperature in this country is much higher than it is in our mother land. The whole question of poisonous milk will come up for future and more detailed study when we write about infantile diarrhea.

A special form of food poisoning at present giving us in this country considerable anxiety is botulism, and to this we devote the following chapter.

Bibliography

- BANKS, J. T.: Dublin Quart. Jour. of Med., 1846, i, 267.
BERNSTEIN, H. S., AND FISH, E. S.: Jour. Am. Med. Assn., 1916, lxvi, 167.
BUCHANAN, A.: Report on Lathyrism in the Central Provinces, Nagpur, 1904.
BUCHANAN, W. J.: Jour. Trop. Med., 1899, i, 261.
SAVAGE, W. G.: Food Poisonings and Food Infections, 1920, Cambridge University Press.
SAWYER, W. A.: Jour. Am. Med. Assn., 1914, lxiii, 1537.
SCHUCHARDT: Deutsch. Archiv. klin. med., 1887, xl, 312.
STOCKMAN, R.: Edinburgh Med. Jour., 1917, New Series, xix, 277.
VAUGHAN, V. C., AND McCLYMONDS, J. T.: Jacobi Festschrift, p. 108.
VAUGHAN, V. C., AND NOVY, F. G.: Cellular Toxins, Philadelphia, 1902, Lea Bros. & Co.
VAUGHAN, V. C., AND PERKINS, G. W.: Archiv. f. Hygiene, 1896, xxvii, 308.

CHAPTER IX

BOTULISM

SAUSAGE POISONING; ALLANTIASIS

Description.—Botulism is a specific form of food poisoning due to a true toxin elaborated by the bacillus botulinus, of which there are at least two types. It is held at present that the bacillus botulinus is an obligate saprophyte, that it cannot grow and multiply in the animal body, and that it is harmful only through the toxin which is produced by the growth of the bacillus in the food before it is eaten. There is still some doubt about the possibility of this bacillus causing a true infection in man and animals. Some observers report that the injection of toxin-free cultures into the abdomen of a guinea pig will kill and that the bacillus has been recovered from the spleen and liver of this animal. It is generally agreed, however, that the administration of even larger doses of some cultures by way of the alimentary canal are without effect.

For quite a hundred years botulism, or, as it was first known, sausage poisoning, has been distinguished from other forms of food poisoning. In 1828 Dann stated the differences in the symptoms between poisoning with food which has undergone putrefactive changes and poisoning with sausage, or, as we now call it, botulism. We have modified Dann's statements, bringing them in conformity with recent observations, and reproduce them in Table III.

In botulism, gastrointestinal disturbances are infrequent or slight and transitory. There may be nausea and vomiting, and this may continue for a day or two. Active purgation is very seldom present and when this does occur it is transient and is followed in practically all instances by most obstinate constipation. According to van Ermengem, the most constant and characteristic symptoms of botulism are as follows: (1) Arrest of the secretions or hypersecretion of the saliva and of the mucus of the buccopharyngeal cavity. (2) Ophthalmoplegia, external and internal, more or less complete blepharoptosis, mydriasis, paralysis of accommodation, diplopia, internal strabismus. (3) Dysphagia, aphonia, obstinate constipation, and retention of urine. (4) A general enfeeblement of the contractile power of all voluntary muscles. (5) The absence of fever, of sensory troubles and of interference with the intelligence. (6) Troubles of respiration and circulation which may cause death more or less rapidly from bulbar paralysis. (7) The characteristic symptoms

TABLE III

POISONING WITH PUTREFACTIVE PRODUCTS	BOTULISM
(1) Period of incubation is usually from two to four hours.	(1) Period of incubation is usually from twelve to twenty-four hours.
(2) Burning in throat and stomach rare.	(2) Burning in throat and stomach frequent.
(3) Dryness and redness of mouth rare.	(3) Dryness and redness of mouth constant.
(4) Constipation never.	(4) Constipation always (although occasionally preceded by temporary diarrhea).
(5) Always purging.	(5) Purging absent or present only in beginning.
(6) Difficult respiration rare.	(6) Difficult respiration frequently observed.
(7) Voice rarely affected.	(7) Voice frequently affected.
(8) Croupous cough never.	(8) Croupous cough very often.
(9) Pulse weak, scarcely perceptible, and frequently rapid (100 to 140).	(9) Pulse weak, scarcely perceptible, often slow (50 to 60). In American cases pulse often rapid (100 to 150).
(10) Heart beat hastened, otherwise not changed.	(10) Heart beat often not perceptible, frequently slow.
(11) Sensorium often cloudy; delirium and sopor.	(11) Sensorium always clear even to death.
(12) No paralytic symptoms.	(12) Paralytic symptoms frequent.
(13) The motility of the tongue is not disturbed.	(13) The motility of the tongue is often disturbed and movements of the tongue are difficult.
(14) Speech not disturbed.	(14) Speech frequently disturbed.
(15) No difficulty in swallowing, or but seldom.	(15) Difficulty in swallowing frequent.
(16) In no case is there ptosis of the upper eyelids.	(16) Ptosis of the upper eyelids is common.
(17) Amblyopia very rare.	(17) Amblyopia very frequent.
(18) Double vision very rare.	(18) Double vision very frequent.
(19) Dilatation of the pupils not rare.	(19) Dilatation of the pupils very frequent.
(20) Ringing in the ears frequent.	(20) Ringing in the ears rare.
(21) The motility of the extremities not disturbed.	(21) The motility of the extremities greatly weakened.

do not manifest themselves until from twelve to twenty-four hours after eating the spoiled food, although they may be preceded by temporary gastrointestinal disturbances. This authority states the symptoms of botulism are so uniform that a diagnosis can be made from these alone.

It is a question whether the toxin of botulism ever induces nausea and vomiting, and it is held by some that when there is evidence of gastrointestinal irritation the food contains putrefactive bodies in addition to the toxin.

Glancy gives an account of his own symptoms after he had partaken of a meal containing bad beef with forty other men at a mining camp in Alaska. Of the forty-one who partook of this meal, twelve died, eight were sufficiently ill to be sent to hospital, and three were slightly incapacitated. Some who ate of the beef were not affected, and this is

accounted for on the supposition that the meat was not uniformly cooked and that it was most rare, and consequently contained the most poison, near the bone. Glancy noticed nothing wrong in himself until twenty-eight hours after the meal, when he observed a certain haziness over his eyes. During the second day after the meal he felt as though he was walking on air. That evening he attended a dance and felt himself all right when in motion, but on resting found marked dimness of vision. The poisonous meal was taken on Thursday, May 22, and he continued his hospital work until Saturday, May 24. His subsequent experience is detailed as follows:

“On entering the hospital my pulse was 73 and temperature 98.4°. Every symptom so far mentioned seemed to be increasing in severity and along with this, extreme muscular weakness. Constipation was marked from the onset. I went to bed at once upon admittance, rested well and noticed no new symptoms that day. The following day (Sunday) I noticed that my eyelids were drooping slightly, my pupils were dilated and diplopia was more marked. Was very restless, and perspired a great deal Sunday night and on into the early hours of Monday. I began at this time to have some difficulty in swallowing. By Tuesday my throat, particularly the right side of the soft palate, pharynx, and uvula, seemed paralyzed. I could scarcely swallow at all and my voice was reduced to a whisper. My throat became clogged with a thick, glairy, tenacious mucus, which I had great difficulty in expelling. My tongue was becoming thick posteriorly at this time. The weakness of my muscles in general was becoming such that I found it an effort to move my limbs in bed. I noticed that my right arm was weaker than my left, though normally it is the reverse. In the following couple of days the above mentioned symptoms all became more severe, it was almost impossible to raise my right hand to my head, I could get my left there with much less difficulty. The extensor muscles of my forearm and hand were particularly affected, also the supinators and pronators of the hand, the flexors were not affected proportionately. Of the fingers the middle and ring fingers were affected most, I am referring here to the right hand and arm. The left side was weak, but the muscles affected were not marked off so distinctly in groups. My tongue now had a thick grayish-black coating and my breath was very bad. Any difficulty I had had up to this time in relation to breathing seemed to be a result of the mucus; now, there was added to this extreme muscular weakness and a paralysis, I believe, of the respiratory mechanism. I could see no expansion of the chest at all, and it seemed like a leaden weight. It was at this time in my illness that I had a period of about twelve hours in which my condition, from a respiratory standpoint at least, was considered the worst. My pulse was of very small volume but regular in rhythm, the rate varied from 88 to 100, my usual rate being 80. My temperature remained normal throughout this bad spell. Following this I perspired freely and was able to breathe more easily. About twelve hours later I had a similar attack but not quite as severe, the whole condition of general weakness, excessive mucus in the throat, difficult breathing and weakened heart prevailed as in the former one, however. The only other new symptom following this, up to the time that I noticed an improvement in my condition, was a severe left-sided headache. Although there had been periods which were not as distressing as others yet I believe the first real step toward recovery occurred on June 8, approximately two weeks from date of admittance, when I found that the left side of my throat (which was only slightly affected at most) felt almost normal. There

was a trifle less mucus forming and it was not as thick and tenacious, while swallowing became a little easier. I was able also, for the first time, to walk to the foot of the bed, holding on to the side. My legs were not affected to the same extent as my arms by any means, but they were very weak also. No symptoms mentioned previously had entirely disappeared up to this time. On June 9, I sat up in a chair for half an hour. Any nourishment which I had had up to the present had been in the form of broths; tomato soup, whites of eggs, milk, brandy, champagne, and brandy-saline enemata. I now began to add a little more to my dietary and to exert myself just a little more each day. On June 11 (eighteenth day in hospital), a dull pain came on in the aortic and pulmonary areas, this continued present to the same degree until June 22, which was the first time that I got a really noticeable expansion of my chest; until now my breathing had been all abdominal and that limited. Up to this time I had lost twenty pounds. From this time on there was a very gradual improvement in every way, and I left the hospital on July 5 to recuperate at a friend's home. By the last of July the pain in the pulmonary and aortic areas had practically gone, I still had some ptosis and lack of expression, was also very easily tired and required to walk with a cane all the time."

In many instances, scintillations before the eyes, dimness of sight and double vision are early symptoms and not infrequently the patient consults a doctor for the first time on account of his eye trouble. The older writers on sausage poisoning state that occasionally complete blindness results. Müller has collected from the literature eleven cases of this kind. Difficulty in swallowing is often a very trying condition. It is in part due to the lack of secretion in the mouth and moist food is swallowed more easily, although difficulty in swallowing is in part due to muscular paralysis. Ulcerations, and even membranes, in the pharynx have been reported, but it is more than likely that these cases were complicated with diphtheria. On account of the difficulty in swallowing, strangulation may become alarming and aspiration pneumonia is not unknown. The speech may be so greatly disturbed that it becomes unintelligible, though, as a rule, it is lisping, slow, and husky. The collection of mucus in the upper air passages leads to a croupous cough, which may be most distressing and may persist for days. In many cases there is more or less marked paralysis of the muscles of the pharynx and larynx. This may be more marked on one side than on the other.

Inhibition of the secretions is a prominent manifestation of the action of this poison. As a rule, the skin is dry and soon becomes rough and harsh. The dryness of the mucous membrane of the alimentary canal apparently extends from mouth to anus. The motility of every part of the alimentary tract is lessened. The stomach lies an immovable organ, discharging its contents in neither direction, so that it has happened that parts of the poisonous food eaten may remain in this viscus for many days. The obstinate constipation is due to paralysis of the walls of the intestines and its relief is difficult. The testimony concerning the effect

of this poison upon the renal secretion is not always along the same line. In some cases there has been reported an excessive flow, while in others this secretion is diminished, and in extreme instances may be entirely suppressed. Most of the early authors reported a slow pulse and compared it with that observed in poisoning by digitalis. In cases occurring recently in this country, there have been great variations in the rate of the pulse, but, as a rule, it is high, generally above 100, and in some instances going as high as 150 per minute. The motility of the heart muscle, in common with all the muscular tissue of the body, both voluntary and involuntary, is impaired, and the beat is weak.

In uncomplicated botulism, the temperature is below the normal, averaging between 96° and 98° F. When the temperature begins to go above the normal, bronchopneumonia may be suspected and it is by this disease that many cases of botulism terminate. On account of the partial paralysis of the muscles of respiration, this function is impaired more or less, the breathing may become shallow, irregular, and there may be marked dyspnea, in fact, death supervenes in many cases from asphyxiation.

While complete paralysis of the voluntary muscles is rare, more or less impairment of their function is common. The patient continues possessed of full intelligence and realizes the growing weakness which is creeping over his whole body. Dickson says:

“The general appearance of the patient is most distressing. The extreme muscular weakness, the anxiety and the utter helplessness, the difficulty in swallowing, the attacks of strangling, the struggle for breath, and the unsuccessful attempts to articulate, constitute a clinical picture which, when once observed, can never be forgotten. The face is usually pale, but in the early stages may be congested. There may be normal appetite and excessive thirst, but the patient is afraid to try to swallow. At times the strangling spells are so severe that there is an incontinence of urine, and an accumulation of thick, tenacious mucus in the pharynx is a constant source of annoyance. The fact that the patient remains in full possession of his mental powers and can realize the seriousness of his condition only adds to the distressing character of the situation.”

The duration of the disease is widely variable. It depends upon the size of the dose of the toxin, the readiness with which it is absorbed, the possibility of some of it being expelled by vomiting or through diarrheal discharges, and possibly upon other unknown conditions. In severe cases recovery is gradual and slow. Kerner reports a case in which on the seventy-fifth day of the disease the heart beat could not be felt, and on the eighty-fifth day the skin remained dry and parched. In some of these prolonged cases, there is marked desquamation of the cuticle. In others, skin infections occur and boils and ulcers result. In most fatal cases, death occurs by the tenth day and some writers state that one who lives to the tenth day is quite sure to recover. There has been more than one recorded exception to this rule and deaths have been reported after

three weeks and even longer. As we have already stated, many cases terminate in bronchopneumonia, manifesting all the symptoms of this disease during the last hours and its lesions after death. Kerner reports slow death through inanition, due to inability to swallow food or to digest it, or to overcome the constipation.

History.—In 1869 Müller collected and abstracted the literature on sausage poisoning. We shall follow this author, making such additions as are to be found in more recent reports and which are deemed worthy of attention. For nearly 200 years past, Württemberg has had the reputation of being the birth place and home of this form of food poisoning. It is more than probable that in the early reports, botulism was sometimes confounded with trichinosis and possibly with other forms of food poisoning. The first article on sausage poisoning dates from 1735 and it was believed that the active agent consisted of some metallic poison coming from the copper vessels in which the food was prepared. From 1789 frequent reports on poisoning with sausage in Württemberg began to attract the attention of the outside world. In 1793 in the village of Wildbad thirteen persons partook of sausage; all were ill and six died. The verdict in this case was that, while the sausage might have had some deleterious effect upon the individuals eating it, the deadly agent was belladonna, which, by accident or intention, had been added to the food. In 1799 several families suffered from sausage poisoning within a short time at or near the village of Mosburg. In one family every member was seriously ill and four died. One son who recovered was accused of adding the seed of henbane to the food. In 1802 official notice was taken of sausage poisoning in Württemberg. A warning was published and instructions given as to the preparation of this article of diet in such a way that it would not be harmful. In this official communication it was stated that the untoward symptoms and death were not due to mineral poisons, but it was suggested that they might be caused by some vegetable poison which was added to the sausage in order to flavor it and render it more pleasing to the palate. The people were warned against the use of certain imported condiments. In 1815 Kerner, a medical man skilled in chemistry and a native of Württemberg, undertook to solve the riddle. He published in 1820 his first monograph, entitled, "Recent Observations on Cases of Poisoning so frequently seen in Württemberg after the use of Smoked Sausage." This was followed two years later by a monograph in which the author satisfied himself that he had found the poisonous agent in the fatty acids contained in the sausage.

In his first report Kerner collected 76 cases, with 37 deaths, and in his second communication the number of cases had grown to 155 and the number of deaths to 84. Kerner states, however, that it is not probable that all cases in Württemberg were reported and that frequent instances

of sausage poisoning probably occurred in the more remote and sparsely settled parts of the Black Forest. It is generally stated that Kerner attributed the harmful action of sausage to the presence in this food of certain fatty acids. This is true in part, but if we read him correctly, he believed that the fatty acid was combined with some nitrogenous substance in which the poisonous properties resided. He states that in all probability the fatty acid in bad sausage is combined with a putrefactive alkaloid to which the great activity of the substance is due. He put most of his work, however, upon attempts to isolate the fatty acids. In carrying out his procedures he extracted the sausage with potash, thus saponifying the fatty acids. To these alkaline extracts he added sulphuric acid in order to set the fatty acid free and then resorted to distillation to obtain his final product. With the distillate he made many experiments upon animals and convinced himself that he produced in these, symptoms quite closely allied to those manifested in individuals who had eaten poisonous sausage. With our present knowledge it is easy to see that by this method Kerner destroyed the toxin which we now know to be the active agent in botulism. In some of his work Kerner employed aqueous extracts of the bad sausage and applied small quantities of this to his tongue, causing a burning sensation in the mouth and throat. It is highly probable that these symptoms were due to the fatty acids, but Kerner, as we now know, was wrong in jumping to the conclusion that because he had found the cause of one of the symptoms he had solved the whole question. About the time that Kerner was carrying on his experiments it was suggested by Emmert that the active agent in poisonous sausage is hydrocyanic acid. This announcement was based largely upon the fact that in persons dead from eating poisonous sausage the blood was found to be fluid and dark in color; in fact, there was no basis whatever for even the suggestion that the active agent might be hydrocyanic acid. This is one of the most rapidly fatal of all poisons, while in sausage poisoning many hours and even several days often elapse before the first symptoms develop. This would be an impossibility if the poisonous or active substance was hydrocyanic acid. Kastner found in the distillates obtained by Kerner's method, acetic and lactic acids and was inclined to agree with Kerner in believing that these acids were combined with a nitrogenous base which was poisonous. Buchner obtained from bad sausage an ethereal oil to which he ascribed the poisonous action. He believed that in the sausage these acids were combined with the oil. Dann, whose valuable study of the symptomatology we have already referred to, came to the conclusion that the fatty acids were combined with empyreumatic oil and he believed the active agent in poisonous sausage to be acrolein. About 1830 it was suggested that poisoning with sausage might be due to diseases in the animals fur-

nishing the meat and much was made of the wisdom of Moses in forbidding the chosen people to eat pork. Soon it became known that sausage is not the only meat that might be poisonous and that identical symptoms do occasionally result from eating not only ham and bacon, as well as sausage, but from foods prepared from the flesh of cattle, sheep, and deer. So much was said about the possibility of the untoward symptoms resulting from the flesh of sick animals that for a while attention was paid to the effects on man of eating the flesh of animals sick with, or dead from, anthrax. Müller collected nearly 100 authenticated cases in which people had eaten the flesh of animals killed while suffering from anthrax. Out of 92 such cases, well authenticated, 10 died, but the symptoms did not correspond with those observed in botulism. The anthrax food caused marked gastrointestinal irritation, with prolonged and exhausting purging. In some instances malignant pustules formed in the inguinal and axillary glands. In no case were the nervous symptoms characteristic of botulism, in evidence. Furthermore, on autopsy, there was no resemblance between anthrax poisoning and sausage poisoning. In the former, section showed marked inflammation of the stomach and intestines, which is never found in botulism.

It is especially worthy of note that in the long continued studies of sausage poisoning and the many discussions which these occasioned, a clear distinction was almost invariably made between botulism and other forms of food poisoning. Müller collected the literature bearing on 100 cases of cheese poisoning and pointed out how this differs from sausage poisoning. He writes that in cheese poisoning the duration of the disease is short and in the majority of instances there is complete recovery even without medical help within from eight to ten hours. In rare instances, the untoward symptoms may continue for 24 hours and death from cheese poisoning is exceedingly rare, Müller finding only one case and that of a child two years of age. In cheese poisoning the symptoms are practically confined to the gastrointestinal tract; purging is present in nearly every case and obstinate constipation is seldom or never seen. The period of incubation is short and paralytic symptoms are never in evidence. Double vision rarely appears and ptosis palpebrarum never occurs. In 1835 Röser, after making careful autopsies of several cases of fatal sausage poisoning, reported that he found the walls of the bronchi and of the small intestine bluish-red in color and attributed this condition to partial paralysis of the capillary vessels. This author held, on account of the slowness with which the symptoms develop and the long continuance of the disease, that the causal agent could not be a mineral or a vegetable poison but must be something capable of growth and reproduction.

For a time it was held that only smoked sausage proved to be poison-

ous and attempts were made to account for the development of the poison by the processes used in smoking the meat. It was suggested by Serres that the poisonous principle might be pyroligneous acid, and by Lusanna that it might be creosote, these substances being rendered more poisonous by their combination with some constituent of the sausage. In 1852 Schlossberger discarded all previously advanced theories and suggested that the poison might be a volatile alkaloid resembling nicotin. About this time Heller had ascertained that the phosphorescence, sometimes observed in decaying meat, is due to a low form of vegetable life, which he named *Sarcina noctiluca*. Following along the same line, van den Corput described a *Sarcina botulina* which, in his opinion, by its growth in the sausage elaborated the poison. This view was attacked by Schlossberger, who called the *Sarcina botulina* a fantasy and a hypothetical growth. Hasselt agreed with Schlossberger in attributing the poisonous action of the food to an acid, which he described as *acidum botulinicum* and which he believed to be combined with a highly poisonous basic substance.

Müller collected some valuable information concerning the symptomatology of sausage poisoning. Of 140 cases, he found that the first symptoms in 124 appeared within 24 hours after eating the food, most of these appearing between 18 and 24 hours. In 7 cases, the first symptoms occurred on the second day; in 15, on the third; in two, on the fourth, and in one each, on the eighth and ninth days.

In 149 cases, 106 complained of pain in the bowels. This symptom was absent in 28 cases and not mentioned in 15. There were nausea and vomiting in 122, not present in 15 and not mentioned in 12. In 127 cases, there was difficulty of swallowing in 101, no symptom of this kind in 10 and not mentioned in 16. In the same cases there was constipation in 101 and temporary diarrhea in 62. The most constant gastrointestinal symptoms were nausea, vomiting, pain in the bowels, and constipation. The oral cavity was generally dry, the gums, tonsils and mucous membrane generally reddened. In most instances burning in the throat was complained of. The diarrhea, if present at all, was temporary and was followed, usually not later than the third day, by obstinate constipation. The most constant symptoms referable to the nervous system were partial paralysis of the muscles supplied by the cranial nerves, and general muscular enfeeblement. Sleep was generally restful, but in some there was observed an appearance and sensation of drowsiness without real or restful sleep. Amblyopia was marked in 93 out of 127 cases and double vision in 85 out of 127. The pupils were dilated in 88 and for the most part not responsive to light. Ptosis palpebrarum was marked in 71 out of the 127 cases. There was marked disturbance in the motility of the muscles of deglutition in 108 out of 149

cases. The flow of saliva was arrested in 101 cases out of 127 and the skin was dry in 79 of these. In 80 out of 127, the voice was affected and in some there was complete aphonia.

Müller speaks of the symptoms as occurring in two stages. The symptoms appear on an average between 18 and 24 hours and those of the first stage consist of general malaise, pressure and pain in the region of the stomach, loss of appetite, nausea, vomiting, and severe pain in the bowels, accompanied sometimes by distention of the abdomen. Accompanying these symptoms are belching, dryness in the throat, and a heaviness in the head. In some cases the patient finds it necessary to support the head and to turn it from one position to another with the aid of the hands.

In the second stage, which usually begins on the second or third day after eating of the poisonous food, there is vertigo, uncertainty in gait, dilatation of the pupils and difficulty in respiration. Diarrhea, if present, is followed by constipation. Cloudiness of vision, double vision, and dysphasia come on. On the third or fourth day there is ptosis of the upper eyelids. The pupils are dilated and not responsive to light. There is progressive paralysis of the esophagus and fear of death from threatening asphyxia. A croupous, unproductive cough results from the accumulation of mucus in the trachea and throat. From the fourth to the tenth day in many instances the dysphasia passes into aphasia. All the secretions with the exception of the urine and milk are, in part at least, suppressed. Vision gradually disappears and may be completely obliterated. Sensation in the ends of the fingers is dull, the tongue becomes lame, the voice is reduced to a whisper, the heart beat can no longer be felt, and the skin is cold. The paralyzing weakness in the arms and legs increases, the movements of respiration become imperceptible, dyspnea passes into apnea and death follows, accompanied by or preceded by light convulsive movements.

We have already stated that in a great many cases the symptoms of the first stage, as given here, are wholly wanting and the first evidence of anything wrong with the individual comes with the development of the nervous symptoms.

The older authors paid great attention to the physical properties of poisonous sausage, hoping thereby to lay down some rules by which this food when bad could be recognized. On this point there are many interesting and not a few contradictory statements. Schlossberger says that there is nothing in the appearance, smell or taste of poisonous sausage by means of which it can be recognized and its harmful quality first manifests itself after it has been eaten. Kerner generally found something wrong with the smell or taste of bad sausage. However, he recog-

nized the fact that the average peasant was not finicky about his food and was likely to eat what a more careful person would reject. After her master had eaten heartily of a sausage the maid pronounced it unfit and threw it to the hogs. The man died but the hogs survived. Scattered throughout the literature are many statements such as the following: "The sausage smelled bad and did not have a good taste." "On account of its bad taste it was quickly swallowed." A housewife, on opening a blunzen (a large sausage) took from its interior a cheesy greenish mass and showed it to her husband suggesting that it should be thrown away, but he devoured the especially offensive part and in due time died, while the remainder of the family ate of the outer portions and were in no wise ill. It is not uncommon to find in the records that in the interior of the sausage there were found mushy, greenish, ill-smelling masses. There are all kinds of descriptions of the odor. It is described as "sour," "like bad cheese," "vile," and "stinking." Schlossberger was the first, so far as we have found, to designate the odor as that of butyric acid. It is more than probable that those who in the early days were poisoned by sausage had never heard of butyric acid.

Although Schlossberger found nothing peculiar in the taste of the poisonous sausage with which he worked, others have stated that it was rancid, sharp, acid, and sticky, and one states that it tasted like garlic.

Many experiments were made upon the lower animals with widely variable results. For the most part, however, animals were not seriously affected. Kerner gave a quarter of a pound of poisonous sausage which had an ill smell and an acid taste, to a dog. The animal ate it, soon vomited it, but swallowed it again, suffered from diarrhea, was apparently ill the following night, but as sound as ever the next day. Weiss apparently killed mice by feeding them poisonous sausage. The experiments on animals, like the chemical examinations, were often made not with what remained uneaten of the sausage, but of portions taken from the original stock; and, quite naturally, in many instances these parts were not poisonous. Attempts were made to compare botulism with other diseases and the list in these comparisons is a long and varied one. Lebert made probably the most sensible comparison when he stated that sausage poisoning resembles in many respects poisoning with belladonna. Sobernheim by some twist came to the conclusion that it resembles cholera. Weiss compared it with typhus fever and, strange to say, Kerner thought it had some relationship to cretinism. However, most of the observers, even in the earliest records, recognized the fact that botulism is a disease *sui generis*. There were many postmortem examinations made in the early days, but the records of these are of but little value. Congestion

in the blood vessels of the mucous membranes was put down by some as inflammation, while others gave it a correct interpretation.

It may be of interest to say a few words concerning the treatment of botulism employed before the discovery of the toxin. On this point there seems to have been among those most competent to speak upon the subject a fair uniformity of opinion. Early evacuation of the stomach and intestines was insisted upon. Emetics were recommended even in cases to which the physician was called for the first time after the development of the nervous symptoms. The reason for insisting upon the use of emetics was that in cases of death even after many days, some of the harmful food was still found in the stomach. When the condition prevented the use of an emetic, the employment of the stomach pump or tube was recommended. It was found that cathartics had but little effect and high irrigation of the intestine was approved by all authorities. So far as the treatment could be directed to the destruction of the poisonous substance in the stomach, chlorin water was used, with the idea that it would not only stop fermentation, but might destroy any poison already formed and still unabsorbed. Some used iodine in potassium iodide solution (*aqua iodata*) in the hope that it would precipitate and render inert any alkaloidal poison that might be present. The agreement concerning the selection of remedies to mitigate the nervous symptoms was not so close. Phosphorus, arsenic, sulphur, strychnin, and belladonna were tried, but no one claimed that marked benefit resulted.

During the greater part of the eighteenth century and the first part of the nineteenth, when botulism was believed to be confined to Württemberg, there was much discussion concerning the method of preparing sausage meat employed in that country. From time immemorial the German peasant has relied largely upon sausage as his meat supply during the winter. He possessed one or more hogs which fattened during the summer and early fall on acorns, nuts, berries, and did not disdain any creeping or crawling thing which came under the eye on the surface or was reached by the snout under the surface. With the coming on of winter, the freezing of the ground and the hiding away of snakes, lizards, mice, moles, etc., the pig could no longer retain the fat which it had accumulated and was now ready for slaughter. The animal was knocked into insensibility by a blow upon the head with some blunt instrument, a vessel in the neck was opened, and every drop of blood was caught in some receptacle, for there could be no loss of food; every part of the animal must be preserved. The carcass was immersed in a hogshead of water, heated with stones which had been piled upon an open fire. After this the hair was plucked by hand. The firmer portions, shoulders, hams, sides, etc., were packed in a chest and

freely covered with salt. The alimentary tube from the cardiac end of the stomach to the rectum was cut into pieces, the natural contents removed more or less completely, the links of intestine, large and small, together with the stomach, were packed with a great variety of animal and vegetable foodstuffs including the blood which had been saved in the slaughter of the animals. In these links were stowed away blood, chopped and ground liver, brain, peas, beans, etc., all mixed with dried leaves, such as sage, and other condiments. These great links, called "blunzen," were hung in the chimney of the peasant's home, from which they were taken link by link as the necessities of the family for food might demand. During the daytime these suspended blunzen were often heated, the outer portions at least, to a temperature sufficient to prevent bacterial growth, but during the night when the fire went out the masses of sausage often froze. It was suggested that this alternate freezing and thawing might be a factor in the development of the poison. As a rule, no harm came from this food until spring, when the links which had been hanging in the chimney for months were reached and served at the table. For this reason it happened that sausage poisoning first appeared to be a seasonal disease. We can now understand how well fitted these conditions were for the growth of the bacillus botulinus and the development of its toxin. Kerner and his colleagues were fully aware of the fact that the poison is more abundant in the interior of the sausage mass than in the peripheral parts; indeed, it not infrequently happened that those who ate of the outer portions of the mass were not at all affected, while those who consumed the inner portions died. In other words, these early investigators learned that the development of the poison occurs under anaerobic conditions, and this has been confirmed by the latest investigations. Some of these older physicians were keen enough to make note of the fact that the poison was not likely to be found in sausage links which were not packed full and which contained air. These procedures in the preparation of the winter's meat apparently have been practiced by German tribes as far back as written records go. The Emperor Leo, known as "The Wise" and as "The Philosopher" (886-911 A.D.), issued an edict under the title, *Ne ex Sanguine Cibus Conficiatur*, in which he stated that the knowledge having come to his majesty's ears that certain people within the empire were in the habit of packing links of intestines with blood and subsequently eating it, the honor of the empire cannot permit such criminal procedure due to the gluttony of man. He, therefore, ordered that anyone who should be found thus preparing and eating blood preparations should be stripped to the skin, severely flogged and banished from the country.

On going over the earlier German literature on botulism one is struck

with the accurate observation of symptoms and the clearness with which this disease was distinguished from all others. Before trichinae had been recognized a differential diagnosis founded on symptomatology had been clearly made between trichinosis and botulism. The main points are set forth in Table IV.

TABLE IV

TRICHINOSIS	BOTULISM
(1) The earliest symptoms appear after forty-eight hours, generally later, and consist of gastrointestinal disturbances.	(1) Symptoms usually appear between twelve and twenty-four hours and consist of gastrointestinal disturbances.
(2) When the number of trichinae introduced into the body is small indigestion symptoms fail altogether or appear late.	(2) The secondary symptoms of intoxication usually appear on the second or third day.
(3) There may be constipation during the first days, but after this there is long continued diarrhea.	(3) There may be diarrhea for the first few days and this is followed by prolonged constipation.
(4) Sometimes the disease begins with diarrhea.	(4) Sometimes the disease begins with constipation.
(5) By the seventh, sometimes, not until the tenth, day there is edema of the eyelids and later of the face.	(5) No edema of either eyelids or face.
(6) No paralysis of the upper eyelids.	(6) Paralysis of the upper eyelids in all severe cases.
(7) Frequent conjunctival catarrh, with redness and infiltration of the cornea.	(7) No conjunctival catarrh.
(8) The secretion of the tears is not arrested.	(8) The secretion of the tears is arrested.
(9) The eyes are not dry.	(9) The eyes are dry.
(10) Response to light is increased.	(10) No response to light.
(11) In many, but not in all, cases the pupil is dilated.	(11) In all cases the pupil is widely dilated.
(12) Pain in the eyes when moved, especially when turned upward.	(12) No pain on movement of the eyes.
(13) No paralysis of the eye muscles, but not seldom there is difficulty in movement on account of inflammation.	(13) Paralysis of motion of the eye muscles is common. There is never inflammation.
(14) Double vision rare.	(14) Double vision frequent.
(15) Fever in all cases.	(15) Fever very rare.
(16) The pulse beats from 70 to 130.	(16) The pulse usually ranges from 40 to 60.
(17) The heart beat is strong.	(17) The heart beat is scarcely perceptible.
(18) There is an evening elevation of pulse and temperature.	(18) No evening elevation of pulse or temperature.
(19) The temperature ranges from 38° to 41°.	(19) The temperature is below normal.
(20) There is great thirst.	(20) Thirst is moderate and sometimes absent.
(21) Sleep is not restful and sleeplessness is the rule.	(21) Sleep is in most cases restful.
(22) The muscles of the neck and back and those of the joints swell and are painful on movement.	(22) There is no swelling of the muscles or pain either at rest or in movement.

TABLE IV—*Continued.*

TRICHINOSIS	BOTULISM
(23) Rest is found only by lying on the back with the extremities slightly flexed.	(23) Any position is comfortable.
(24) There is usually profuse perspiration.	(24) Perspiration is seldom observable.
(25) The skin is always moist.	(25) The skin is always dry.
(26) Frequently there are exanthems, urticarial and often miliary.	(26) Exanthems are never observable.
(27) Sometimes there is slight delirium.	(27) No delirium.
(28) The patient lies on his back, motionless, with flexed arms and legs. The face, especially the eyelids, is swollen.	(28) The patient sits, walks, or lies as he pleases. Only in the most severe cases is he confined to bed. Every position is possible. Face and eyelids are not swollen.
(29) The arms and legs cannot be extended without pain and the mouth cannot be opened wide.	(29) The arms and legs can be extended without pain and the mouth can be opened wide.
(30) The patient complains of pain in the arms, legs, and back.	(30) There is no pain in the extremities or in the back.

After the discovery of trichinae the microscopic examination was found sufficient to make a differential diagnosis.

Since 1870 reports of outbreaks of botulism in Germany have not been so frequent and the inference has been drawn that on account of more scientific methods of food preparation this accident has become rare in that country. Bitter, writing in 1919, states that botulism in Prussia is not rare and that the number of cases is much larger than the official reports indicate. In 1904 Fischer reported an outbreak at Darmstadt, which is of special interest, inasmuch as for the first time the presence of the toxin was recognized in a food which contained no meat. The fatal dish consisted of a bean salad prepared in a cooking school and canned three months before it was served. When the can was opened it was noticed that the contents had a rancid odor, which became more pronounced on the addition of vinegar, but the food was only rinsed and was served without being heated. Of the 21 people who ate of this salad, all were ill and 11 died. A strain of bacillus botulinus was obtained from these beans and yielded a toxin which killed guinea pigs in doses of 0.0003 c.c. Savage says (1920) that he is unable to trace the existence of a single outbreak in Great Britain.

Recently (1922) there have been in Great Britain several outbreaks of botulism. Meyer has found the spores in English soil.

A great advance in our knowledge of botulism was made by van Ermengem, who obtained cultures of bacillus botulinus from a ham which in 1895 caused illness in 23 persons, with three deaths, at Ellezelles, Belgium. Aqueous extracts of the ham and cultures of the bacillus induced classical symptoms of botulism in monkeys, rabbits, cats, guinea

pigs, and pigeons. Van Ermengem ascertained that this bacillus is a saprophyte and that its harmful effects are due to a true toxin which is elaborated under anaerobic conditions in the food before it is consumed. A discussion of this bacillus, its toxin and the antitoxin will follow later.

Geiger, of the Public Health Service, has kindly furnished us with the following list of outbreaks of botulism known to have occurred in the United States and Canada:

HUMAN BOTULISM IN CALIFORNIA

H. C. = Home Canned, Com. = Commercially Canned.

"A"—Single cases or those occurring in groups or families proved by Bacteriologic and Toxicologic Tests.

				Cases	Deaths
1. String Beans	(H. C.)	Jan. 1916,	San Jose	1	1
2. String Beans	(H. C.)	Jan. 1917,	Escondido	7	4
3. Spinach	(Com.)	Oct. 1920,	Oakland	6	3
4. Spinach	(Com.)	June 1921,	San Diego	1	0
5. Apricots	(H. C.)	Jan. 1918,	Madera	8	6
6. Corn	(H. C.)	Jan. 1917,	Corning	1	0
7. Olives, Minced	(Com.)	Feb. 1920,	Richmond	1	1

"B"—Clinically typical cases single or in groups and families, causative food assigned on epidemiologic grounds only.

				Cases	Deaths
8. String Beans	(Com.)	May 1910,	Oroville	4	4
9. String Beans	(H. C.)	1912,	Amador Co.	6	5
10. String Beans	(H. C.)	Nov. 1913,	Stanford Univ.	12	1
11. String Beans	(H. C.)	July 1916,	San Pasquale	1	0
12. String Beans	(H. C.)	Feb. 1918,	Los Angeles	1	1
13. String Beans	(H. C.)	Feb. 1918,	Oakdale	1	1
14. String Beans	(H. C.)	May 1918,	Fresno	1	1
15. String Beans	(H. C.)	Dec. 1919,	San Rafael	4	4
16. String Beans	(H. C.)	Dec. 1919,	Los Angeles	1	1
17. String Beans	(H. C.)	Jan. 1920,	Los Angeles	1	1
18. String Beans	(H. C.)	Apr. 1920,	Los Angeles	1	1
19. Ripe Olives	(Com.)	Feb. 1920,	Los Angeles	1	0
20. Minced Olives	(Com.)	Oct. 1918,	Napa	2	2
21. Minced Olives	(Com.)	Dec. 1920,	Los Angeles	5	0
22. Apricots	(H. C.)	March 1915,	Fallbrook	5	5
23. Apricots	(H. C.)	Jan. 1918,	San Bernardino	2	2
24. Pears	(H. C.)	Jan. 1910,	Sawtelle	12	11
25. Pears	(H. C.)	March 1918,	Colton	1	0
26. Asparagus	(H. C.)	Nov. 1915,	Sacramento	1	1
27. Corn	(Com.)	Apr. 1918,	San Rafael	1	0
28. Homebrew		Sept. 1919,	Colusa	5	4
29. Tamale (beef)		May 1899,	Los Angeles	1	0
30. Beef		Nov. 1902,	San Francisco	7	3
31. Calf's Head					
Vinegarette	(H. C.)	1913,	Los Angeles	1	1
32. Pork and Beans	(Com.)	Dec. 1906,	Los Angeles	3	3
33. Ham (Home cured)		Oct. 1917,	Los Angeles	2	2
34. Sausage	(Com.)	Jan. 1915,	Los Angeles	2	2
35. Clam Juice	(Com.)	Oct. 1913,	San Francisco	2	2
36. Clam broth	(Com.)	1912,	San Jose	2	1
37. Tuna	(Com.)	Feb. 1918,	Los Angeles	1	1
38. Probably fish pickled in vinegar	(H. C.)	July 1921,	San Jacinto	1	1
39. Cottage Cheese	(H. C.)	June 1912,	Long Beach	7	2

"C"—Cases of Botulism—causative food unknown.

				Cases	Deaths
40.	Anatomically	May	1916, San Francisco	1	1
41.	or Bacteriologically proved	April	1921, San Luis Obispo	1	1
42.			1913, Hornbrook	1	1
43.	Clinically proved	March	1913, Los Angeles	1	1
44.		Nov.	1919, Berkeley	3	0
45.		Sept.	1920, Corning	1	0

HUMAN BOTULISM IN WASHINGTON

"A"—Single cases or those occurring in groups and families proved by Bacteriologic and Toxicologic Tests.

				Cases	Deaths
46.	String Beans	(H. C.)	Feb. 1921, Seattle	1	1
47.	Asparagus	(H. C.)	Nov. 1917, Seattle	3	3
48.	Spinach	(H. C.)	May 1919, McKenna	3	3
49.	Corn	(H. C.)	April 1921, Yakima	1	1
50.	Corn	(H. C.)	Jan. 1916, Yakima	1	1
51.	Corn	(H. C.)	Nov. 1917, Yakima	1	1
52.	Corn	(H. C.)	Dec. 1918, Yakima	1	0
53.	Asparagus	(H. C.)	Nov. 1910, Yakima	6	3
54.	Spinach	(H. C.)	April 1921, Yakima	2	2
55.	Milk	(Com.)	Oct. 1920, Yakima	4	0
56.	Asparagus	(H. C.)	Oct. 1921, Walla Walla	1	1
57.	Corn	(H. C.)	Oct. 1921, Yakima	1	1

"B"—Case Clinically Typical

				Cases	Deaths
58.	Unknown	Nov.	1919, Monroe	1	1

HUMAN BOTULISM—UNITED STATES AND CANADA, OUTSIDE OF CALIFORNIA AND WASHINGTON

"A"—Single cases or those occurring in groups and families proved by Bacteriologic and Toxicologic Tests.

				Cases	Deaths
59.	Ripe Olives	(Com.)	Aug. 1919, Canton, Ohio	14	7
60.	Ripe Olives	(Com.)	Oct. 1919, Detroit, Mich.	7	5
61.	Ripe Olives	(Com.)	Jan. 1920, New York City	5	5
62.	Ripe Olives	(Com.)	Feb. 1920, Memphis, Tenn.,	7	7
63.	Ripe Olives stuffed with Pimento	(Com.)	Nov. 1919, Java, Montana	7	5
64.	Ripe Olives	(Com.)	June 1921, Greensburg, Pa.	3	3
65.	Spinach	(Com.)	Jan. 1921, Grand Rapids, Mich.	29	3
66.	Spinach	(Com.)	Jan. 1921, Battle Creek, Mich.	5	2
67.	Spinach	(Com.)	Feb. 1921, Mishawaka, Ind.	2	2
68.	Corn	(H. C.)	Oct. 1915, Hillsboro, Ore.	1	1
69.	Asparagus	(H. C.)	Jan. 1918, Boise, Idaho	4	4
70.	Beets	(Com.)	May 1920, Florence, Arizona	5	5
71.	String Beans	(H. C.)	Feb. 1918, Decatur, Indiana	7	4
72.	Ham (Preserved at home)		1916, Tampa, Fla.	7	7
73.	Sausage (Home prepared)		1912, Lowell, Mass.	4	4
74.	Summer Sausage	(Com.)	Dec. 1919, Milwaukee, Wis.	3	0
75.	Cottage Cheese (Home prepared)		Oct. 1914, Rural N. Y. State	3	3

"B"—Clinically typical cases, single or in groups and families, causative food assigned on epidemiologic grounds only.

76. String Beans	(Com.)	1915, Basalt, Colo.	?	5
77. String Beans or Spinach	(Com.)	Oct. 1912, Romley, Colo.	7	5
78. String Beans	(H. C.)	Dec. 1917, Ontario, Ore.	1	1
79. String Beans	(H. C.)	Oct. 1918, Klamath Falls, Ore.	1	1
80. String Beans	(H. C.)	March 1918, Newark, N. J.	3	2
81. Corn	(H. C.)	Nov. 1917, New York State	7	5
82. Corn	(H. C.)	Jan. 1920, Pittsburgh, Pa.	4	3
83. Beets	(H. C.)	April 1921, Pueblo, Colo.	5	3
84. Possibly Beets	(Com.)	May 1919, Dawson City	23	12
85. Tomato Catsup	(Com.)	? Cook Co., Ill.	2	0
86. Spinach	(Com.)	April 1920, New York City	2	2
87. Minced Chicken	(?)	May 1913, Boston, Mass.	1	0
88. Ham	(Com.)	June 1920, Maine	4	4
89. Smoked Ham and Salted Pork (Home prepared)		Nov. 1919, Sioux Rapids, Ia.	5	3
90. Unknown		May 1916, Boston, Mass.	1	0
91. Unknown		April 1918, New York City	1	0

THE FOLLOWING IS A LIST OF THE LATEST OUTBREAKS
(UNCLASSIFIED)

				Cases	Deaths
92. Spinach	(Com.)	March 1922, Kendalville, Ind.		8	4
93. Spinach	(Com.)	Jan. 1922, Canaan, Ohio		2	2
94. Corn (Home canned in pressure cooker)		Feb. 1922, Wieser, Idaho		1	1
95. String Beans	(H. C.)	Dec. 1921, Grants Pass, Ore.		1	1
96. String Beans	(H. C.)	Jan. 1922, San Francisco, Cal.		2	2
97. String Beans	(H. C.)	Feb. 1922, Healdsburg, Cal.		3	3
98. Spinach (Beet and Turnip Tops Home canned)		Jan. 1922, Cambridge, Idaho		8	6
99. Corn	(H. C.)	March 1922, near Cheyenne, Wyo.		1	1
100. Corn	(H. C.)	May 1922, Near Yakima, Wash.		1	1
101. Unknown		May 1922, Livermore, Cal.		1	1
102. String Beans	(H. C.)	May 1922, Templeton, Cal.		1	0
103. Chili Sauce	(H. C.)	June 1922, Watsonville, Cal.		2	2

The symptoms of botulism as manifested in this country are practically identical with those long known and closely studied in Germany. It seems that the pulse rate in cases in this country is frequently much higher than that given in the classical German writings. Most of the European authors say that the pulse rate is low, frequently from 40 to 60. In this country it frequently runs as high as 150.

We have excluded from the above list all cases in which there has been continued fever. One such case is that reported by Lewis, in which fever persisted for five and one-half weeks, the temperature curve going as high as 105° and falling as low as 96°. In this instance there were certain well-marked symptoms of botulism, such as diplopia, ptosis, and

dysphagia. This may have been a case of botulism, but if it were, in our opinion, it was complicated with some other disease.

The Sawtelle cases reported by Peck were due to home canned pears. These had been prepared by the mother in the preceding September and in January, 1910, they were served as the special dessert at a family dinner. About 24 hours after the dinner Peck first saw the mother and infant child. He found the woman sitting in a chair, holding the child in her lap, and gives the following description of her condition:

"The woman's head seemed to be loose upon her shoulders when she tried to move it; marked incoordination of the muscles of the neck was strongly in evidence. Her head was bowed partially upon her chest, in which position she held it most of the time. Her cheeks bore a slight deadly flush, but did not indicate fever. Her eyes were almost closed; the lids appeared to be wearied. Her general appearance gave the impression of life struggling with death in a losing battle. The mouth was slightly open, from which, with her handkerchief, she was continually removing the fast forming saliva, which was quite thick and tenacious. Upon examination of her tongue, it appeared thicker than normal and was evidently slightly paralyzed. She moved it with difficulty. It was covered with a heavy white, foul coating. She complained of her throat, saying that it felt badly, and that she could not swallow without difficulty. She could not swallow even a teaspoonful of water without choking violently. She was asked if she felt any pain in any part of her body and she replied that she did not, only some aching above the eyes. She complained that she could not see good and that there was a mist before her eyes. Upon examination the pupils were found dilated, but accommodation at this time appeared nearly normal, but reflex to light was quite deficient. Her temperature was slightly subnormal, pulse 120, weak but regular; respiration between 25 and 30 and quite irregular. She talked with great difficulty. The action of the kidneys, as near as could be ascertained, was and had been fairly good. The skin was slightly moist, rather cool, and felt unnatural. There was no recognizable paralysis of the arms, hands or lower extremities, but incoordination was evident when she arose and attempted to walk. Vomiting had occurred but once, slightly and only with the first symptoms. Elimination by the bowels had become *nil*, neither could it or vomiting be induced from this time forward by any course of treatment to any extent, so far as to be of any practical benefit. The woman presented the appearance of laboring under the influence of extreme alcoholic intoxication, except that her intellect was clear, and her ideas presented in a perfectly normal manner. She was persuaded with difficulty to go to bed, and when she was placed there she refused to lie down and was placed in a reclining position, supported with pillows. * * * After the patient was placed in bed she slowly grew weaker, the pulse slightly more rapid and weak, the respiration more frequent and about two hours before the end she fell gradually into a quiet and peaceful slumber, but which lacked the impress of a normal repose. She died at 10:30 p. m. on the next day."

In the 11 fatal cases resulting from this outbreak, the average time from eating the pears until the first symptoms were observed was about 23 hours; the minimum, two hours for a boy of eight years who had eaten three helpings of the pears, and the maximum, 30 hours. The average time from eating the fruit until death was 40 hours; the maximum, 63, and the minimum, 25.

The Colorado cases reported by Curfman showed the typical symptoms of dizziness, diplopia, ptosis, dilatation of the pupils, paralysis of accommodation, difficulty in swallowing and talking, with eventually complete aphonia in the fatal cases, marked in all by general weakness and constipation. The temperature was subnormal, but the pulse rate was above 100. Two died within 48 hours; one on the third day; one on the sixth day, and one two weeks after eating the canned spinach. In one of the cases which recovered, the patient was unable to comb her hair for four weeks and could not walk without assistance for six weeks. Indeed, three months after the poisonous meal this patient was unable to read or to do any close work. Curfman states that five burros that ate the remnants of this meal died after developing symptoms similar to those observed in the patients.

Botulism in Animals.—Graham and his coworkers have apparently demonstrated that certain forms of so-called forage poisoning in horses and mules are in reality botulism. As early as 1901, it was suggested by Pearson that forage poisoning in domestic animals might be a form of botulism and this was emphasized by Mohler in 1914. The first experimental work along this line was done by Buckley and Shippen in 1916. A full discussion of this subject will be found in the reports by Graham and his confreres. They found that *B. botulinus* administered to horses and mules in wholesome food causes symptoms and lesions closely resembling, if not identical with, those recognized in natural outbreaks of forage poisoning as seen in central Kentucky. *B. botulinus* grows and develops its toxin in corn silage, alfalfa and corn extracts when made slightly alkaline. Anaerobic organisms resembling *B. botulinus* were obtained from horses dying of forage poisoning. Antitoxin prepared against *B. botulinus* protected guinea pigs against the toxin of the organisms found in the silage. Graham and his companions are quite certain that the organism found in silage and to which certain cases of forage poisoning are due, is closely related to, and is probably a strain of, the *B. botulinus* which is responsible for food poisoning in man. It seems that in silos there is enough carbonic acid generated to reduce the oxygen content sufficiently to permit of the growth of the anaerobic bacillus botulinus. This is a matter both of public health and of economic importance. If the researches of Graham turn out as they now promise, there will be opportunity for the saving of the lives of many animals. It is stated that in Missouri alone thousands of mules die yearly from forage poisoning. It is probable that forage poisoning includes not only cases of botulism, but other diseases as well.

Graham and Schwarze have extended these studies and applied them to cattle. They found an anaerobic bacillus biologically related to *B.*

botulinus (Type B) in corn silage. A herd of 18 cattle feeding on this silage developed symptoms of forage poisoning and four of the animals died. When the remaining animals were withdrawn from this food they regained their health and continued free from any evidence of disease. An antitoxin prepared from *B. botulinus* (Type B) protected guinea pigs against lethal doses of the toxin produced by the anaerobic bacillus isolated from the corn silage.

Geiger is of the opinion that certain forms of forage poisoning in horses are probably true botulism. He says that spoiled vegetables, or ensilage, caused four different outbreaks in which the presence of *B. botulinus* and its toxin was proved indirectly by immunization experiments or by the coincident occurrence of botulism in human beings or fowls. Chickens often die in large numbers from feeding upon discarded food containing the toxin. Botulism in cats, dogs, goats, and hogs is rare, though cases have been reported.

The Bacillus.—While there are certain morphologic and biologic variations in the different strains of bacillus botulinus, they have enough in common to render a general description fairly accurate. This bacillus is a large one, from 4 to 9 microns in length and from 0.9 to 1.2 microns broad. Generally the ends are rounded and often two or more individuals are attached end to end, occasionally forming long threads. In hanging drops in the presence of air these bacilli show a slight motility. They carry from four to eight flagella, distributed along the sides. They are gram-positive, but in decolorizing care must be taken that they are not left too long in the alcohol. In various oxygen-free media and at temperatures ranging from 20° to 35° C. they form spores, generally at the ends, more rarely in the middle. When grown under hydrogen in glucose gelatin they form round, transparent, slightly yellow colonies consisting of slightly motile individuals. These colonies are surrounded at first by small fluid zones; later they become more brown, lose their transparency, and show thorn-like projections. In still older cultures, the edges of the colonies are nicked and are marked by more or less branched extensions.

Stick cultures in glucose agar or gelatin evolve large quantities of gas, which breaks up the medium. In the gelatin tubes there is complete liquefaction with the formation of foam. At the same time the bacilli, in the form of large white floccules, sink to the bottom, leaving the liquefied gelatin perfectly clear. In oxygen-free glucose bouillon the growth of this bacillus is at first cloudy but later becomes clear, giving off during this process more or less abundant quantities of gas, which consists of hydrogen, carbonic acid, and methane. In oxygen-free bouillon containing milk or cane sugar instead of glucose, there is only

a moderate growth and no evolution of gas. Van Ermengem recommends for abundant growth and the production of active toxin, a medium consisting of finely chopped meat and water, equal parts, with the addition of 2 per cent glucose, 1 per cent pepton, and 1 per cent common salt. This medium should be rendered slightly alkaline, covered with a layer of fat or vaselin, boiled, rapidly cooled, and then inoculated. In this medium growth rapidly proceeds, with the abundant evolution of gas, at from 25° to 30° C. In bouillon gelatin or agar, or in media which do not contain grape sugar, growth is less abundant, involution forms appear and the bacillus dies in a short time. Cultures of this kind are not markedly toxic. In order to obtain a highly toxic culture, van Ermengem used a medium prepared from a calf's liver. He also found that fairly abundant and toxic cultures could be prepared from an exclusive vegetable medium, such as green peas, potatoes, beans, etc., to which a little pepton and common salt were added. If to these vegetable preparations grape sugar is added, the production of gas is more abundant and the elaboration of toxin more in evidence.

Meyer and his coworkers, after many experiments, have chosen as most suitable for the enrichment of *B. botulinus* a preparation made as follows: (1) Take 1,000 grams of finely ground, fat-free beef heart; stir in 1,000 c.c. of tap water; slowly heat to boiling; adjust to a reaction of P_H 8.0-8.2; then cool and skim off the supernatant fat. (2) Wash and mince finely five or more large pigs' stomachs with an equal amount of pig's or beef liver according to the following formula: Minced pig's stomach, 400 grams; minced liver, 400 grams; hydrochloric acid (Baker Chemical Company), 40 grams; tap water at 50° C., 4,000 grams.

Keep the mixture in glass or porcelain receptacles for from 18 to 24 hours. When both the biuret and tryptophan tests become positive the digest has a green yellowish color and contains but little undigested debris. Transfer to large bottles and steam for ten minutes in order to arrest digestion. Strain digest material through cotton or allow to stand overnight in the ice-chest and decant after 24 hours. Warm the decanted digest to 70° C. and neutralize with sodium carbonate to litmus at this temperature. Filter the desired amount. Add .2 per cent dibasic potassium phosphate. Adjust to P_H 7.4 and to two parts of this preparation add one part of No. 1. Adjust the final reactions and sterilize for one hour at 18 pounds pressure. Incubate for five days and repeat sterilization at the same pressure. Meyer says:

"The beef heart peptic digest liver broth can be autoclaved without inducing changes in the reaction or in the growth supporting and enhancing properties of the enrichment mediums. The optimum reaction of this medium is a P_H of 7.0-7.4. * * * Repeated attempts to isolate *B. botulinus* in a pure state from positive enrichment cultures in van Ermengem's medium were either not successful or were in comparison with those

made from beef heart mediums considerably more difficult. The principle of selective heating could not be applied to these cultures, probably on account of the absence of or the low heat resistance of the spores. These and other observations led to the routine use of beef heart peptic digest liver broth for the enrichment and demonstration of *B. botulinus*."

Although *bacillus botulinus* is an obligate anaerobe and is best grown when all oxygen is excluded, it will thrive in media in the presence of certain other bacteria which consume the oxygen. It grows well in the presence of air, provided that there be in the culture white sarcines, *bacillus subtilis*, oxygen consuming organisms. In these preparations the formation of toxin is as abundant as when the bacillus is grown in pure cultures. It has been shown by Tarozzi that *bacillus botulinus* can apparently be grown as an aerobic organism, provided there is added to the bouillon tube a small piece of a fresh aseptic bit of animal or vegetable tissue, such as a piece of the liver or kidney of a guinea pig or a small piece of recently boiled potato. These tissues absorb and hold the oxygen in the tube, in this way permitting the anaerobic *bacillus botulinus* to grow. We have already seen that this bacillus will grow and produce its toxin in silos and this is due, partially at least, to the presence in the fodder of oxygen consuming microorganisms. In part, it is probably due to the driving out of the oxygen by carbonic acid gas and other gaseous products of fermentation taking place in the silo.

Meyer and his coworkers find that *B. botulinus* can grow in an environment which contains about two-thirds atmospheric oxygen. Loosely packed damp hay or soil inoculated with spores will become toxic in the presence of air. Pure and mixed cultures grow abundantly in the beef heart digest broth, even when it is not stratified with vaselin or freed from air, by heating before inoculation. Such growths furnish toxins varying in potency from 10,000 to 50,000 m.l.d. per c.c. for 250 gram guinea pigs.

It was found by van Ermengem that the optimum temperature for the growth of *bacillus botulinus* lies somewhere between 25° and 30° and at these temperatures the organism grows most abundantly and produces the largest quantities of toxin. According to the early experiments, growth and the production of toxin at temperatures above 30° C. were feeble, while at 37°, even in glucose containing media and in the absence of oxygen, growth was found to be exceedingly slow, with the formation of long threads passing into involution forms and with the production of only traces of toxin. It is quite evident that the different strains of this bacillus are not uniformly influenced by temperature. Armstrong, Story and Scott, in studying the bacillus in ripe olives which poisoned people at Canton, Ohio, found that this organism grew best and produced the most toxin at a temperature of 37° C. Tubes grown at

this temperature for nine days developed a toxin approximately 200 times as strong as an eleven-day culture grown at room temperature. The sterile filtrate from this nine-day culture grown at 37° proved fatal to guinea pigs in doses of 0.00005 c.c. when administered intraperitoneally. In several other outbreaks in this country it has been found that the organism grows abundantly and produces toxin in large quantity at 37°.

In a comparative study of over 100 strains of *B. botulinus* from various sources Meyer and his confreres have shown that the optimum temperature for growth and toxin production is 35° C. In the beef heart digest medium the maximum potency of the toxin is reached on from the tenth to the twelfth day of incubation at 35° C.

The reaction of the medium on which the best growths are obtainable seems to vary with the strain. Van Ermengem found the Elzevelles strain did not grow on media having a decidedly acid reaction, and, indeed, required a certain degree of alkalinity for the highest production of gas and the formation of the most active toxin. Other observers have worked with strains which require for their best production a slightly acid reaction, and, indeed, it appears that the same strain from time to time varies in its susceptibility to the reaction of the medium in which it grows. Possibly the influence of other constituents of the medium may intensify or nullify, as the case may be, the effect of the reaction. It is of practical importance that we should get all the information possible concerning the influence of the percentage of common salt in the medium as it affects the growth of *bacillus botulinus*. A small amount, from 0.5 to 1 per cent, of common salt in the medium, seems essential to the growth of this bacillus, but the upper limit or the amount of common salt necessary to entirely inhibit its growth is not determined with so much certainty. It seems fairly safe to say that *bacillus botulinus* will not grow and, consequently, will not develop its toxin in brines containing as much as six per cent of common salt; at least, up to the present time no strain has been found which will grow and produce a toxin in brines of this strength.

As has been stated, *bacillus botulinus* is a spore producing organism. Van Ermengem found that the spores of this bacillus are killed at unusually low temperatures, not surviving 85° for more than one-quarter and 80° for more than one-half hour. Apparently, however, this is not true of all strains. The Canton, Ohio, strain was found to be an abundant producer of spores which were quite resistant to heat. Tubes heated to 100° C. for thirty minutes in an Arnold sterilizer when incubated at 37° showed growth and gas formation on the fourth day; indeed, in order to destroy the spores of this organism it was found necessary to heat for

a long period at 100° or to autoclave at fifteen pounds for fifteen minutes. In old cultures the spores retain their vitality for a long time, even when the reaction has become decidedly acid. There is no reason why spores of this organism in canned foods might not retain their vitality for years; indeed, this has been found to be the case in cultures in fused tubes when protected from light. The bacteriologist, desirous of keeping his cultures active, should make transplantations every four to six weeks.

It will be seen from these statements concerning the biology of *bacillus botulinus* that it is an organism especially adapted for growth in canned foods. It will thrive on most, if not all, foods that are thus prepared. It will grow quite as well and produce toxin just as abundantly on fruits as it will on meats. Certain strains at least, apparently grow better on fruits than on meats. The Canton strain was not only found in ripe olives, but it proved to grow abundantly on these olives when they were chopped, sterilized and inoculated. The *bacillus botulinus* grows not only on fruits and meats, but it yields equally rich harvests when planted upon vegetable preparations, such as spinach, peas, beans, etc.; in short, there seems to be no food material upon which this organism will not grow and in which it will not produce a toxin, provided air is excluded and time enough is given for the elaboration of the toxin.

Bigelow thinks that it is not true that *B. botulinus* grows readily in fruits. He holds that ripe olives are not a typical fruit. They have a very low acidity when they are harvested and are then soaked in sodium hydroxid solution to remove the tannin until the alkali reaches the pits. The alkali is removed largely by washing with water and the juice of the fruit is left neutral or slightly alkaline. Bigelow gives as his impression that *B. botulinus* will not grow in any of our ordinary fruits. He says that it is true the records show that several outbreaks of botulism were caused by home canned fruits, but he thinks the fruits used in these cases were partially decomposed to start with, and he is quite certain that our statement that certain strains of *B. botulinus* apparently grow better in fruits than in meats is an error.

Geiger, in summarizing one of his case reports, makes the statement that botulism can be prevented by thoroughly cooking all canned vegetables or fruits which have not been previously processed at high temperatures, after they are removed from the container.

As van Ermengem pronounced after his first studies, *bacillus botulinus* is a pathogenic saprophyte. Botulism is an intoxication and not an infection. The *bacillus* produces the toxin in the food before it is eaten and not in the body after the organism has been taken in. Although it has been shown that the spores of certain strains may resist a tempera-

ture of 100° there is still no evidence that multiplication of the organism takes place in the animal body. It should always be borne in mind that it is not easy to remove all the toxin from an infected food by washings; indeed, this method of separating the toxin from the bacillus has been tried. In the experiments made with the Canton strain the organism was subject to 14 separate washings in order to remove every trace of the toxin without success. It will be seen from this that it is practically impossible to wash a food sufficiently to free it from any contained toxin.

The question of the resistance of the spores of this organism to heat is a matter of such practical importance that it is desirable to give greater detail concerning it. Burke has tested the thermal death point of the spores of ten strains and finds that, while exposure to a temperature of 100° C. inhibits or retards the development of the spores of *B. botulinus*, it does not kill them. The sterilizing processes of the cold pack are not sufficient to kill the spores. One heating in boiling water for five minutes will not sterilize the contents of jars if they are contaminated with the more resistant spores. Fractional sterilization on three successive days, after exposure to a temperature of 100° for from 15 to 60 minutes, retards but does not prevent the development of the organism. Pressure canning is the safest method of sterilization, but a pressure of as much as 15 pounds for ten minutes will not kill the more resistant spores. It is important that housewives be warned of the danger of spoilage and should be cautioned to examine every jar carefully when it is opened for use. The signs of spoilage are as follows: (a) The presence of gas bubbles in the jars and of blown heads and of squirting of liquid when the top is removed; (b) the odor of rancid cheese; (c) the mushy appearance of the solid parts of the food in the jars. The toxin produced in canned foods may be destroyed by boiling for five minutes or longer, although the spores are not killed. It is the toxin in the food and not the spores that causes botulism, because the spores do not multiply in the body. The only safe procedure is to discard every can presenting one or more of the evidences of decomposition mentioned above.

Meyer says:

“It is fully proved that any lot of canned food which shows an appreciable percentage of spoilage is potentially dangerous, but no laboratory has as yet determined the percentage of containers of such lots which may harbor viable spores of *B. botulinus*. Until such tests have been carried out every can or jar of a batch or lot showing even less than one per cent spoilage must theoretically be considered suspicious. It is definitely proved that the presence of *B. botulinus* in canned food is always indicative of poor sterilization and a few recent investigations have disclosed that not one container, but usually the entire lot or pack, has been improperly processed.”

Burke, Elder and Pischel make the following statements concerning the care that must be exercised in the selection of preserved foods:

“(1) Spoiled foods containing gas may appear to be boiling for several minutes before the true boiling point is reached. We recommend that all suspected foods be subjected to vigorous boiling for at least thirty minutes before being tasted. (2) Spoiled canned foods giving the appearance of boiling for seven minutes and subjected to actual boiling for four minutes are not safe to eat. Spoiled canned foods exposed to a temperature of 80° C. for one hour may appear to be boiling part of the time and not be safe to eat. (3) We may expect to have outbreaks of botulism following the eating of insufficiently cooked spoiled foods. (4) The heat resistance of the disease-producing power of different kinds of spoiled canned foods containing *B. botulinus* and its toxins has not been determined and probably will be found to vary. (5) There have been no recorded outbreaks of botulism in this country without a history of preserved foods having been eaten. (6) There is no evidence that infection in man ever follows the ingestion of toxin-free organisms of *B. botulinus*. (7) There is no evidence that infection in man ever follows the ingestion of the toxin and organisms of *B. botulinus*. (8) Botulism does not result from the ingestion of small numbers of toxin-free spores.”

The distribution of *B. botulinus* in nature is a matter of great importance. This subject was investigated in California by Burke in 1918. She made an attempt to find this organism in five localities in which cases of botulism from home canned foods had been reported. She found the organism in the following substances: (1) Bird-pecked, bruised, and moldy cherries; (2) bean leaves covered with spots or droppings of insects or small animals; (3) on spiders from bush bean plants; (4) on bush beans, some of which were slightly scarred, picked over, washed and packed in clean jars; (5) manure from a hog which had recovered from botulism three months before the sample was taken; (6) in moldy hay from an outdoor stack upon which horses and mules had fed and subsequently developed symptoms of forage poisoning. Burke concluded that *B. botulinus* is widely distributed in nature and that it may be present on fruits and vegetables when they are picked. Burke's experiments were confined to localities in California, but the work of Graham and others has demonstrated that this organism is widely distributed throughout the country and that botulism is likely to occur from the eating of canned food prepared in any infected locality. There is, however, no danger from eating fresh fruits or vegetables wherever grown. In doing so, one may take into the stomach the bacillus, but it is not accompanied by any toxin and it is to this toxin that botulism is due.

Meyer and his colleagues have made some astonishing discoveries concerning the geographical distribution of the spores of *B. botulinus*. Strange to say, these spores have been found by these investigators most frequently and most abundantly in virgin soil, and often in that taken from mountain sides where there has been no evident soil pollution by

either man or animal. The first positive proof of the existence of these spores in virgin soil was furnished by a number of soil specimens removed from a rock slide which occurred on March 1, 1921, about 1,000 feet above the floor of the Yosemite Valley. On the twentieth of the following April these samples were examined and revealed the presence of spores of *B. botulinus* demonstrated in pure culture and by the production of toxin. Identical findings were made with soil collected from an excavation four feet deep in the heart of the valley in which pollution with animal manure, etc., was excluded. These findings have been confirmed by the examination of numerous soil specimens from mountainous regions in California and Washington. In mountain soils and in virgin soils generally Type A predominates or is the exclusive finding. In the soils from gardens, orchards, cultivated and fertilized fields spores of *B. botulinus*, while widely distributed, are not so constantly found as in virgin and mountain soils and, besides, in the cultivated regions Type B predominates. This leads Meyer to suspect that the original and natural habitat of the spores of *B. botulinus* is in mountain soils, from which they are distributed to cultivated and low lying regions by water carriage and that as a result of this transportation and change in environment there is a mutation from Type A to Type B. Fruits and vegetables bought in the open market in San Francisco, San Jose, and Los Angeles showed a contamination with these spores to the extent of 29.4 per cent.

"The findings on the vegetables and fruits correspond in a general way with those made on the soil specimens collected in gardens and cultivated fields. The relatively high percentage of Type B toxins has been repeatedly confirmed by the isolation of *B. botulinus* Type B from the enrichment cultures. The vegetables, such as beets, asparagus, etc., bought in San Francisco were grown in truck gardens heavily fertilized with hog manure. Specimens of the fertilizer were tested for spores of *B. botulinus* with negative results. Soil products procured from plots recently planted with vegetables furnished enrichment cultures, which contained Type A toxins. Invariably the repeated examination of the soil demonstrated the same type. As far as the limited material permits of deductions, it is evident that the products of a soil, which has been manured and cropped for many years, more frequently contains the spores of *B. botulinus* Type B than those of Type A. Fruits and vegetables are excellently suited to demonstrate this distribution, probably on account of the relative minority of other proteolytic anaerobes, which ordinarily destroy the toxins or overgrow *B. botulinus* present in specimens prepared from manured or fertilized soil."

Meyer's studies on the distribution of the spores of *B. botulinus* in the olive groves and on the fruit in its transportation from the orchard to the factory are especially interesting.

"Not only were the leaves and fruits on the trees found to be contaminated, but the scrapings from the shipping barrels transporting the ripe olives from the groves to the cannery, as well as the refuse dumps composed of spoiled, discarded olives, supplied toxic cultures. Furthermore, several tins of ripe pickled olives, processed at low temperatures and unprocessed, so-called 'bulk olives,' gave pure cultures of *B. botulinus*

Type A. The frequent finding of Type B spores only on the foliage and green fruits is closely connected with the predominance of this type in the manured soil of the ranches. This type is probably not very resistant against physical and chemical agents, rarely survives the pickling and preserving process and has, therefore, not been found in the packed products. Seventeen, or twenty-two per cent of the seventy-five olive specimens produced toxic cultures; the proportion of Type A to Type B was one to four. The foliage and green olives collected from the trees furnished ten per cent weakly toxic enrichment cultures. From a practical standpoint, it is beyond question that *B. botulinus* is frequently carried on the ripe fruits into the shipping barrels, pickling vats and the packing plant. * * * It is not unlikely that during and shortly after the War, the collection of ripe olives in the orchards was not conducted with a great deal of care. The raw product, heavily contaminated with soil, underwent further deterioration and the resistant spores were permitted to increase by prolonged storage in shipping barrels and pickling vats. The common practice of preserving olives by heat not exceeding 212° F. produced in some containers an environment suitable for the growth of *B. botulinus* and its toxin. It is, however, now fully recognized that efficient sterilization of fresh, and careful handling of ripe olives will prevent further outbreaks of botulismus.”

While Meyer and his coworkers found the spores of *B. botulinus* widely distributed in hay, straw, and other animal feeds, they do not believe that these findings justify the claim that forage poisoning is due to this organism. Strange to say, the examination of 45 specimens of manure and fertilizer showed the presence of the spores in only 6.6 per cent. The evidence is that *B. botulinus* does not, to any marked extent at least, multiply in the alimentary canal of either man or beast, and that fertilizers in the shape of manure contribute relatively little to the pollution of the soil with this organism. Soil contaminated with animal feces is rarely infected, while mountain and forest soils in California are practically always bearers of *B. botulinus* spores.

It is apparently the custom, at least in some parts of California, to fertilize vegetable gardens with sewage. An outbreak of botulism in chickens caused by eating beans which had grown in a garden thus fertilized led to a search for the spores in the untreated sewage, but the result was negative and there was found no cause to justify the supposition that the beans owed their infection to the sewage. In numerous experiments Meyer was able to demonstrate that human excreta produced, as a rule, nontoxic enrichment cultures irrespective of the fact that the individuals were constantly eating raw fruits and vegetables bearing the spores. This indicates that there is no multiplication of the organism in the alimentary canal of man. It is evident that in California at least, botulism is not disseminated by the excreta of either man or beast. It will be seen that in its biologic behavior *B. botulinus* is radically different from *B. tetanus*, the former being found most abundantly in virgin soil while the latter occurs only in soil infected with the excreta of man or animals.

Meyer and his colleagues have tested soils from practically every state in the Union and from many foreign countries for the presence of spores of *B. botulinus*. The most heavily infected areas, as shown by these analyses, are the mountainous and coast states of the West, including Washington, Oregon, and California, with Utah, Wyoming, and Montana slightly less infected. Pennsylvania and Kentucky show a degree of infection scarcely less than that shown by the Pacific States, but in the East Type B predominates, while in the West it is Type A. The condition found in Pennsylvania and Kentucky strengthens the theory that the normal habitat of the spores of *B. botulinus* is in elevated regions and that the plains below are infected through the transportation of soil by means of rain. A similar condition in the Ozark Mountains in Missouri lends further support to this theory. The greater part of the region roundabout the Great Lakes, along the Mississippi and its tributaries shows a low incidence, not so low however as the area covered by Texas and New Mexico. Meyers concludes this part of his work with the following statements:

“(1) The spores of *B. botulinus* are relatively rare in the samples of soil, etc., collected from the Middle States, the Great Plains, and those bordering the Great Lakes and the Mississippi River with its tributaries, the Missouri, Arkansas and Red, Des Moines and Illinois Rivers. (2) The Atlantic States supplied specimens which produce frequently ten to thirty per cent toxic cultures. (3) The soil of the Pacific Coast and Rocky Mountain States is heavily infected with *B. botulinus*.”

The distribution in Canada, Hawaii, Alaska and China, as shown by the analyses that have been made, corresponds in a general way, so far as it is related to mountains and plains, with that found in the United States.

So far as we know, this is the first evidence that a bacterial disease has its breeding-place in virgin forests and mountains and in which the microorganism loses in virulence after transportation to heavily contaminated soils. This opens up to the epidemiologist a new viewpoint requiring a wider knowledge before he can attempt a satisfactory explanation.

The Toxin.—This toxin resembles that of certain plants, such as castor and jequirity beans, inasmuch as it is active when taken by the stomach, and in this respect it differs from the toxins of the venoms of serpents and of tetanus and diphtheria, which are not active when thus administered. It is true, however, that the toxin of the bacillus botulinus is more poisonous when administered intravenously or hypodermically than when given by mouth, but naturally this form of administration plays no part in food poisoning. Van Ermengem found that rabbits die after from 36 to 48 hours with symptoms of local and general paralysis when a glucose bouillon culture is subcutaneously given in doses of from 0.0003 to 0.001

c.c. In these experiments symptoms may appear within a few hours but are often delayed for three or four days and in either instance lead to death within a few hours. The animals thus treated develop rapid breathing, become paralyzed, manifest clonic convulsions and die with loud outcries. In some cases the paralysis is confined to certain groups of muscles. In some, only the legs, especially the hind legs, are involved. There is abundant and abnormal secretion of saliva, accompanied by dilatation of the pupils, with exophthalmos, aphonia, complete anorexia and retention of urine and feces.

Guinea pigs are still more susceptible to subcutaneous injections and death results from treatment with from 0.0001 to 0.00005 c.c. There is often complete paralysis of all the muscles, respiration is at first rapid and superficial, but later becomes prolonged. After the administration of still smaller doses, symptoms do not develop until the third or fourth day and the paralysis may be confined to one or more extremities. Mice are still more susceptible and die after the development of paralysis from the smallest possible doses.

In monkeys (rhesus) the subcutaneous injection of from 0.01 to 0.001 c.c. causes characteristic symptoms, consisting of dilatation of the pupils, which are often immobile, ptosis of both lids, abundant secretion of a thick grayish mucus from the nose and mouth, accompanied by coughing and followed by aphasia, dyspnea, and death within from 24 to 36 hours.

Van Ermengem found that cats are well suited for the development of experimental intoxication by subcutaneous injection. These animals show paralytic symptoms, accompanied by ptosis, aphasia, aphonia, prolapse of the tongue, abundant elimination of thick mucus from the mouth, with croupous coughing and retention of urine and feces. On the administration of massive doses (5 to 10 c.c.) there is a latent period of from six to twelve hours, followed by collapse, general paralysis, dilatation of the pupils, and death within from 16 to 24 hours.

All the above mentioned animals may be poisoned and caused to develop similar symptoms to those given, by intraperitoneal or intracranial administration. Van Ermengem observed that intracranial injection does not lead to the more rapid development of symptoms than when administration is accomplished by subcutaneous or intraperitoneal treatment.

There have been considerable inexplicable differences observed among animals after administration by mouth. Van Ermengem found mice, guinea pigs, and monkeys best suited for demonstration by this method of administration. Rabbits withstand considerable quantities of the poison when thus administered, but do succumb when large doses (5 to 10 c.c.) are given. The same observer found dogs, rats, and chickens

unaffected by massive doses administered in the food. On the other hand, numerous investigators in this country have found chickens highly susceptible, developing characteristic symptoms of limberneck. Emerson and Collins, using the bacillus which caused the Detroit outbreak, found chickens quite susceptible and highly suitable for the demonstration of the action of this poison.

The toxin is quickly destroyed at a temperature of 80° C. and undergoes more gradual decomposition when exposed to light and air. The toxin is altered but little on the addition of dilute acids, but is rendered inert by strong alkalis. It is not influenced by putrefactive changes in the culture medium. The toxin has been obtained in the dry state by precipitation with zinc chlorid, subsequent decomposition with ammonium phosphate, and precipitation with neutral salts. The toxin thus obtained apparently has lost no appreciable amount of its toxicity and when dissolved and properly diluted it produces in animals the characteristic symptoms and death. Like tetanus toxin, it seems to have a special affinity for nervous tissue, with which it combines and by which it is neutralized.

The Antitoxin.—Kempner was the first to prepare a successful antitoxin. He immunized goats by successive administrations of increasing doses of toxin and obtained a serum which protected guinea pigs against 100,000 minimum lethal doses. Forssman and Lundstrom also immunized goats, employing subcutaneous injections, which they found to be more efficient than intravenous administrations. Since these preliminary studies, horses have been immunized and effective antitoxins in large amounts have been obtained. It has been shown that an antitoxin prepared with one type is not equally effective in affording protection against the toxins produced by the other. Dickson and Howitt conclude a study of the preparation and therapeutic value of botulinus antitoxin with the following statements:

“(1) A true antitoxin may be prepared for the toxin of bacillus botulinus. (2) There are at least two types of *B. botulinus* which are distinct so far as their toxin-antitoxin relationships are concerned. (3) Experiments show that in the laboratory the antitoxin may protect against the action of the toxin for at least 24 hours after the administration of one test dose of toxin, but that the effectiveness is, to a certain extent at least, dependent on the amount of toxin injected. For therapeutic administration a polyvalent antitoxin should be employed, and it should be given in large amounts and intravenously.”

Burke, Elder and Pischel make the following statement concerning the specific treatment of botulism:

“Since there are at least two distinct toxins, and there is no rapid means of determining the type, it is necessary to use a polyvalent antitoxin or a Type A and a Type B antitoxin, and since there is a possibility that *B. botulinus* occasionally

produces its toxin in the body, the immune serum should be bacteriolytic or bactericidal as well as antitoxic. The serum should be injected intravenously. The immune serum to be beneficial must be used as soon as possible after the diagnosis is made. In all cases of doubtful diagnosis, all those having partaken of the suspected meal should receive immediately antitoxin treatment. The antitoxin can only neutralize the toxin and prevent further injury. It is of no value to the already damaged nervous system. The evidence we have indicates that treatment begun after the symptoms are well advanced will not, in most cases, alter the course of the disease. But we have sufficient experimental evidence to believe that some of those receiving lethal amounts of toxin can be saved by the use of antitoxin if the treatment is begun at about or before the time the symptoms appear."

In our opinion the statement made in the last sentence of this quotation is hardly justified.

At present (1922) antitoxin is prepared only in those laboratories in which special research on botulism is being carried out. We understand that there has been no permit from the Surgeon General of the Public Health Service for the preparation of a commercial product. McCaskey used small doses of antitoxin in the treatment of three patients who were poisoned by eating home canned string beans at Decatur, Ind. One recovered and two died. McCaskey believes that the serum was of some aid, but inasmuch as he gave only from 5 to 10 c.c., his conclusion is open to doubt. In the Detroit outbreak, Jennings, Haass and Jennings injected 42 c.c. of Graham's serum intravenously in one case without apparent effect and 20 c.c. in two injections in another patient who recovered. They state, however, that in the latter case the illness was so mild they could not be sure about the influence of the serum on the patient. As to the manner of administration Dickson and Howitt make the following statement:

"It is our opinion that large doses of antitoxin should be given since the amount of toxin ingested is unknown, and that it should be given intravenously. * * * The usual precautions for the administration of horse serum should be observed, and the patient tested by intracutaneous injection for evidence of hypersensitiveness. When no hypersensitiveness is shown, the serum will be given at once and will be injected into the veins very slowly, not more than 1 c.c. a minute, until the full amount is given. When hypersensitiveness is shown, preliminary subcutaneous, intramuscular and intravenous injections of 1 c.c. at one hour intervals should be given, and one hour after the last injection the full amount may be injected intravenously at the rate of not more than one c.c. a minute."

Prevention.—It was not until the War was upon the people of the United States and after the cold pack method of preserving food had been recommended by the U. S. Department of Agriculture that there came the realization of the great danger that lies in the imperfect or incomplete sterilization of preserved foods. Although cases of botulism had been occasionally reported in the United States before that time, Dickson, of California, in 1918, first called the attention of the people

to the danger in the spread of botulism. The problems presented by this relatively new disease, or at least one only recently recognized as of importance, led to immediate activity, especially on the part of the Universities of California and Leland Stanford, with the aid of the U. S. Public Health Service. In August, 1920, the California State Board of Health passed the following resolution:

“Resolved, By the California State Board of Health, that ripe olives shall be deemed adulterated within the meaning of the California Pure Foods Act unless, before being offered for sale or consumption, all picking, handling, cooking and other preparation of the product shall have been carried on in strict conformity with the Food Sanitation Act, sections 1 to 8, inclusive, and that the provisions of this act will be held to apply to all holding solutions, holding tanks, separating trays, curing tanks, curing solutions, as well as to the premises generally, as specified in the act; furthermore, be it

“Resolved, That ripe olives shall be deemed adulterated within the meaning of the California Pure Foods Act unless the same shall have been sterilized at a temperature of 240 degrees Fahrenheit for a period of not less than forty minutes by means of a retort or autoclave which shall be controlled by an automatic self-recording thermometer or heat-measuring device in proper working order, and that the temperature record shall be available at all times to the representatives of the State Board of Health; furthermore, be it

“Resolved, That the Director of the Bureau of Foods and Drugs, California State Board of Health, be instructed to seize and quarantine all ripe olives which are not produced in conformity with the above regulations and to institute action for their condemnation and destruction.”

In 1919 the National Canners Association asked the National Research Council to be responsible for certain scientific investigations on botulism and other forms of food poisoning. The Canners Association has been very active and has appropriated large sums of money for these researches. The problems that have been opened up by these studies have been of great scientific, as well as of practical, importance. Marked improvements have been made in the processes of canning foods and in securing complete sterilization of these products. There can be no doubt that within a short time all reputable organizations engaged in the preparation of preserved foods will be able to furnish safe products. It is well, however, to be on the safe side and there must be vigilance not only on the part of state and municipal health officials, but consumers of canned foods must constantly be alert to detect any evidence of decomposition or spoilage in these food preparations. With our present knowledge, a health officer is justified in withdrawing from sale every can of a product which has been found to be deleterious to health. It has been abundantly demonstrated that the cold pack process, which was recommended during the War, is inadequate in securing complete sterilization. Everybody should plainly understand that it is not safe to even taste of suspected canned food. Death may result from the eating of a single

bean when a can of this food is contaminated with *B. botulinus* and contains the toxin.

Bibliography

- ARMSTRONG, C., STORY, R. V., AND SCOTT, E.: Public Health Reports, 1919, No. 51.
 BIGELOW, W. D.: Personal communication.
 BITTER, L.: Deutsch. med. Wehnschr., 1919, xxxv, 1300.
 BURKE, G. S.: Jour. Am. Med. Assn., 1919, lxxii, 88; Jour. Bacteriol., 1919, iv, 541.
 BURKE, V., ELDER, J. C., AND PISCHEL, D.: Arch. Int. Med., 1921, xxvii, 265.
 CURFMAN, G. H.: Colorado Med., 1917, xiv, 35.
 DICKSON, E. C.: Monograph of the Rockefeller Institute for Medical Research, 1918, No. 8.
 DICKSON, E. C., AND HOWITT, B. M.: Jour. Am. Med. Assn., 1920, lxxiv, 718.
 EMERSON, H. W., AND COLLINS, G. W.: Jour. Lab. and Clin. Med., 1920, v.
 FISCHER, A.: Z. klin. Med., 1906, lix, 58.
 FORSSMAN, J., AND LUNDSTROM, E.: Ann. de l'Inst. Pasteur, 1902, xvi, 294.
 GEIGER, J. C.: U. S. Pub. Health Repts., 1921, xxxvi, 1663; Pub. Health Bull., 127.
 GLANCY, J. A. R.: Canadian Med. Assn. Jour., 1920, x, 1027.
 GRAHAM, R., BRUECKNER, A. L., AND PONTIUS, R. L., Kentucky Agricultural Experiment Station Bulletin, 1917, Nos. 207 and 208.
 GRAHAM, R., AND SCHWAEZE, H. R.: Jour. Bacteriol., 1921, vi, 69.
 JENNINGS, C. G., HAASS, E. W., AND JENNINGS, A. F.: Jour. Am. Med. Assn., 1920, lxxiv, 77.
 KEMPNER, W.: Ztschr. f. Hyg. u. Infectiouskrankh., 1897, xxvi, 481.
 LEWIS, W. M.: South. Calif. Pract., 1899, xiv, 466.
 McCASKEY, G. W.: Am. Jour. Med. Sc., 1919, clviii, 57.
 MEYER, K., ET AL: Unpublished reports.
 MÜLLER, (MINDEN): Deutsch. Klinik., 1869, xxi, 321, 341, 357, 365, 381, 453; *ibid*, 1870, xxii, 27, 35, 49, 97, 115, 123, 154, 171, 197, 229, 248, 263, 276, 286, 301, 321, 327, 334, 343, 354.
 ORR, P. F.: Jour. Infect. Dis., 1922, xxx, 118.
 PECK, G. W.: South. Calif. Pract., 1910, xxv, 121.
 VAN ERMENGEM, E.: Ztschr. f. Hyg. u. Infectiouskrankh., 1897, xxvi, 1.

CHAPTER X

CHOLERA INFANTUM

THE SUMMER DIARRHEAS OF INFANCY; ILEOCOLITIS

Description.—In this chapter we discuss certain diarrheas which have the following common characteristics: (1) They occur only in infants during the first and second years of life; (2) they are practically confined to those children who are artificially fed, not more than five per cent are seen among the breast-fed; (3) their prevalence is determined by weather temperature, rising with the increasing heat of summer and declining with the lowering temperature of fall and winter.

There are wide variations in the symptomatology and pathology of these diarrheas and pediatricians have attempted to classify them according to the extent and depth of the lesions found in the intestinal walls after death. Formerly, the designation, cholera infantum, was generally employed by American physicians to include all these diarrheas. In more recent years this term has been restricted to the more acute, violent, and fatal cases, and the term ileocolitis, modified by certain prefixed adjectives, such as catarrhal, follicular, and membranous, has been substituted. The acute cases are frequently ushered in with marked choleraic symptoms, although these may be preceded by some intestinal disorder. Vomiting and purging, accompanied or preceded by a rapidly rising temperature and leading to speedy and marked prostration, may be the first symptoms in a babe which hitherto has been the picture of health. The evacuations are in the beginning abundant. The first vomitings consist of whatever food there may be in the stomach, while subsequent ones consist of mucus, serum and matter regurgitated from the small intestine. When vomiting ceases for a time it is likely to be renewed whenever food or drink is taken into the stomach. The first stools are large, more or less loose, and occur once or twice in an hour. Later they become greenish, yellowish, or brownish, and finally may lose all color and consist almost entirely of serum. At first, the stools are generally acid, but the reaction changes to neutral and when they become serous they are alkaline. The odor is subject to wide variation, none being perceptible in some, while in other instances they are highly offensive. The flesh melts away rapidly, the eyes are sunken, the angles of the mouth are drawn, and the countenance becomes expressive of the utmost anxiety. While the temperature is variable, it usually rises in proportion to the severity of the case and in extreme instances it may

reach 107° before death. The pulse is irregular, rapid in proportion to the severity of the case, and towards the end becomes imperceptible. These cases certainly deserve to be designated as choleraic, and more than seventy-five per cent of them prove fatal.

The subacute and chronic cases lead to the development of more or less marked and extensive catarrhal, membranous, and ulcerative conditions in the mucosa and submucosa. To the pathologist, it probably seems altogether unreasonable to place these diarrheas in one group and from his standpoint he is right, but to the epidemiologist, they belong, in our opinion, together. Neither in symptomatology nor in pathologic lesions does cholera infantum show more diverse manifestations than those which follow poisoning with arsenic. When many times a fatal quantity of this poison in soluble form, such as the arsenite of potash, is administered, the vital cells of the body, including those of the central nervous system, may be so suddenly and so completely overwhelmed and wrecked that the individual falls without preliminary symptoms into a fatal coma; on the other hand, when the insoluble arsenous oxid is administered there is great variation in the time of onset, in the violence of the symptoms, and in the lesions which are found after death. Finally, when very small doses of arsenic are taken over long periods of time, the first intimation of ill effects may be found in a neuritis or in skin lesions, and yet, all of these are cases of arsenic poisoning and should be grouped and studied as such. For these reasons it is, in our opinion, not inappropriate for the epidemiologist at least, to consider these diarrheas as belonging to the same group etiologically.

We are quite in accord with the following statement, bearing upon this subject, made by Hartshorne, in 1880:

“Until within comparatively a few years, American writers have classed together all cases of what is popularly known as *summer complaint* in children, under the name cholera infantum. Latterly (1870) Meigs and Pepper and others have urged the propriety of separating, in diagnosis and nomenclature, this affection, as a true choleraic disease, from the enterocolitis of infancy, acute or chronic. There is no doubt that many instances of intestinal inflammation occur in children, at all seasons and under many circumstances, to which there is no reason for giving the name of cholera infantum. Rillet and Barthez even assert that, under their observation, of every two young children that die, one exhibits a more or less serious lesion of the large intestine. But there does not seem to be sufficient ground for the narrowness of limitation now mentioned for the term cholera infantum. As described by the authors referred to, enterocolitis occurs, in most cases, under the same combinations of promoting and exciting causes, with the same commencing and closing symptoms, and with the same lesions (differing only in degree, not in kind) as what those authors recognize as cholera infantum.

“Objection appears to be made to the application of this latter designation to cases not attended throughout their duration by violent vomiting, and prostration resembling the collapse of epidemic cholera. But the term cholera, being as old as the time of

Hippocrates, had the meaning of *copious watery flux* long before epidemic cholera had any place in nosological literature. This kind of disorder, then, may well be called choleraic; and, in view of the essential agreement of a large number of cases, in etiology, general semeiology and morbid anatomy, we may safely call by the name of cholera infantum all such attacks as have the following characteristics: Affecting infants during their first or second years, especially at the time of dentition; occurring in towns or populous rural localities in hot weather; attended by vomiting during a portion, but not necessarily the whole, of their course; with diarrhea, acute or chronic, usually producing emaciation and threatening, if not fatal debility.’’

As we shall see later, attempts have been made to find specific bacteria as the causative agents of the summer diarrheas of infancy, but up to the present these investigations, valuable as they have been, have failed to demonstrate a specific bacterial cause for any one of this group of diarrheas. In 1898 Vaughan wrote:

“The studies of the past 15 years have demonstrated that milk poisoning is one of the most fruitful causes of a high death rate. A little more than one-fourth of the children born to the civilized world die before they reach five years of age, and about one-half of these deaths are due to the so-called summer diarrheas. The medical profession sought for the causative factors of these diarrheas for many years in almost every conceivable condition surrounding the life of the infant. Inherited tendencies were considered, and, although these are important factors in the causation of the high death rate of infancy, they are of but slight weight so far as the summer diarrheas are concerned. That the sins of the father and of the mother also, are visited upon the child, often with apparently relentless cruelty, is a matter of every day’s professional observation, but the child of the saint as well as that of the sinner cannot withstand the powerful poisons that may be generated in milk by bacterial life. Long and earnestly did the medical profession study the influence of meteorological conditions upon these diarrheas. The temperature of the air and the soil, the humidity, the proportion of sunshine and cloud, the amount of rainfall, the direction and velocity of the wind, all were studied. Finally, the following conclusions became evident: (1) These diarrheas are practically confined to the hot months; (2) only those who are artificially fed have these diarrheas; (3) since artificial feeding is substantially confined to the employment of cow’s milk, this food must become harmful during the hot months.

“Upon these well observed facts there followed the discovery of most powerful poisons in milk infected with certain bacteria and kept at a temperature high enough for their development. Then followed a search for the specific bacterium of the summer diarrheas, but no specific microorganism for this disease has been found, and none will be found, because any one of a number of saprophytic bacteria is capable of elaborating a galactotoxicon (milk poison). I do not mean to say that two species of bacteria will produce in milk identically the same chemical changes, but they will elaborate poisons which, so far as their effects upon children are concerned, are practically identical. The time may come when the chemist will be able to isolate these poisons, and when this has been done it may be possible by a study of the toxicologic action of each of them to distinguish one from the other by observation of the symptoms. At present, however, this is impossible, and we must study these bacterial poisons as a group of gastrointestinal irritants.”

History.—In 1886 Hirsch wrote as follows, under the head of cholera infantum:

“Acute maladies of the intestinal tract take the first place in the statistics of mortality for the age of infancy; and among these, vomiting and purging carry off most victims in that period of life, under circumstances to be mentioned in the sequel. Cholera infantum, or vomiting and purging in infants, is a comparatively new term insofar as it is taken to denote a form of gastrointestinal lesion peculiar in its pathology and etiology; we meet with it first in the medical writings of the end of the last century or early years of the present. But there can be no doubt that the malady had occurred at all times under the same circumstances that give rise to it now, and that it has become commoner just in proportion as the etiological factors have made themselves felt in a more intense form and over a wider area.

“We can only infer, therefore, as to the past *history of infantile cholera*; and even within the most recent periods, the information about the disease from various parts of the world is so incomplete and untrustworthy, that we can form no certain opinion of its *geographical distribution*. It may be concluded from the facts, but only with a degree of probability, that the disease occurs all over the globe, and that it is always worst where the causal conditions about to be mentioned are most felt.

“The earliest definite accounts of this serious scourge of infancy come from the *United States*. It is to Benjamin Rush that the credit belongs of having been the first to call the attention of practitioners to the disease; although the names that had been given to it for some time before in colloquial speech, such as ‘disease of the season,’ ‘summer complaint,’ or ‘April and May disease’ (southern states), stamp it as a malady already known to the people at large. After Rush’s paper, there began to come in from all parts of the States accounts by medical practitioners of this disastrous malady, the ‘*pestis infantum americana*,’ the writers vying with each other in their attempts to find suitable language for its destructiveness. ‘It is the main outlet,’ says Harrison, ‘to the lives of a great many children every year; and when the rest of the community is comparatively healthy, its ravages invade the sanctuary of infantile feebleness and sweep the fond anticipations of parental love to the grave!’ From these and innumerable later writings, the fact comes out that cholera infantum is everywhere prevalent in the large towns of the North American continent, from Quebec to New Orleans and from the Atlantic to the Pacific; and prevalent to such an extent that Horner has a certain warrant in speaking of it as ‘a disease entirely American.’ In Massachusetts and Michigan the deaths from infantile cholera amount to fifteen per cent of the annual mortality from all causes; in the City of Boston the percentage is 22.18. In New York the deaths from that disease between 1805 and 1837 were nearly two per thousand of the population; and in recent years they have increased considerably. In Philadelphia for the year 1872, the mortality from cholera infantum was reckoned at 2.6 per thousand of the population, while from 1819 to 1860 it amounted to between one-fourth and one-third of the deaths from all causes. It is as high, and sometimes even higher, in Baltimore, Louisville, Natchez, St. Louis (1841-43), Memphis (which has been called ‘the graveyard of children’), and in many other large American cities, including even the Californian towns of San Francisco and Monterey, where King says, ‘more children die of cholera infantum and lobular pneumonia than from any other disease.’ ”

As has been stated, Benjamin Rush is credited with writing, in 1793, the first description of this disease, under the title, “An Inquiry Into the Cause and Cure of the Cholera Infantum.” He wrote as follows:

"By this name I mean to designate a disease, called in Philadelphia, 'the vomiting and purging of children.' From the regularity of its appearance in the summer months, it is likewise known by the name of 'the disease of the season.' It prevails in most of the large towns of the United States. It is distinguished in Charleston, in South Carolina, by the name of 'the April and May disease,' from making its first appearance in those two months. It seldom appears in Philadelphia till the middle of June, or the beginning of July, and generally continues till near the middle of September. Its frequency and danger are always in proportion to the heat of the weather. It affects children from the first or second week after their birth, till they are two years old. It sometimes begins with a diarrhea, which continues for several days without any other symptoms of indisposition; but it more frequently comes on with a violent vomiting and purging, and a high fever. The matter discharged from the stomach and bowels is generally yellow or green, but the stools are sometimes slimy and bloody, without any tincture of bile. In some instances they are nearly as limpid as water. Worms are frequently discharged in each kind of the stools that has been described. The children, in this stage of the disease, appear to suffer a good deal of pain. They draw up their feet, and are never easy in one posture. The pulse is quick and weak. The head is unusually warm, while the extremities retain their natural heat or incline to be cold. The fever is of the remitting kind, and discovers evident exacerbations especially in the evenings. The disease affects the head so much, as in some instances to produce symptoms not only of delirium, but of mania, insomuch that the children throw their heads backwards and forwards, and sometimes make attempts to scratch, and to bite their parents, nurses, and even themselves. A swelling frequently occurs in the abdomen, and in the face and limbs. An intense thirst attends every stage of the disease. The eyes appear languid and hollow, and the children generally sleep with them half closed. Such is the insensibility of the system in some instances in this disease, that flies have been seen to alight upon the eyes when open, without exciting a motion in the eyelids to remove them. Sometimes the vomiting continues without the purging, but more generally the purging continues without the vomiting, through the whole course of the disease. The stools are frequently large, and extremely fetid, but in some instances they are without smell, and resemble drinks and aliments which have been taken into the body. The disease is sometimes fatal in a few days. I once saw it carry off a child in four and twenty hours. Its duration is varied by the season of the year, and by the changes in the temperature of the weather. A cool day frequently abates its violence, and disposes it to a favorable termination. It often continues, with occasional variations in its appearance, for six weeks or two months. Where the disease has been of long continuance, the approach of death is gradual, and attended by a number of distressing symptoms. An emaciation of the body to such a degree, as that the bones come through the skin, livid spots, a singultus, convulsions, a strongly marked hippocratic countenance, and a sore mouth, generally precede the fatal termination of this disease. Few children ever recover, after the last symptoms which have been mentioned make their appearance."

Rush discusses the causes to which this disease had been up to that time attributed. The belief most generally held was that the disease is a result of dentition, but Rush points out that children teethe at all periods of the year, while they have cholera infantum only in the hot months of summer. It had been believed that worms played a part in the causation of this disease, but Rush states that intestinal worms are frequent in children and never cause an idiopathic fever. Moreover, in autopsies

held after death from cholera infantum, it occasionally happened that no worms could be found. The causal importance of summer fruits was easily disposed of, because children on farms eat more fruit and have less cholera infantum than those in cities.

Rush advised, for the prevention of this disease, the following procedures:

“(1) The daily use of the cold bath. (2) A faithful and attentive accommodation of the dresses of children to the state and changes of the air. (3) A moderate quantity of salted meat taken occasionally in those months in which the disease usually prevails. It is perhaps in part from the daily use of salted meat in diet, that the children of country people escape this disease. (4) The use of sound, old wine in the summer months. From a teaspoonful, to half a wine glass full, according to the age of the child may be given every day. It is remarkable, that the children of persons in easy circumstances, who sip occasionally with their parents the remains of a glass of wine after dinner, are much less subject to this disease, than the children of poor people, who are without the benefit of that article of diet. (5) Cleanliness, both with respect to the skin and clothing of children. Perhaps the neglect of this direction may be another reason why the children of the poor are most subject to this disease. (6) The removal of children into the country before the approach of warm weather. This advice is peculiarly necessary during the whole period of dentition. I have never known but one instance of a child being affected by this disease, who had been carried into the country in order to avoid it.”

Creighton in 1894, wrote as follows:

“Infantile diarrhea and the cholera nostras of adults are closely allied in symptoms and pathology, but they are so unlike in their fatality that they are best considered apart. Dysentery is sufficiently distinguished from choleraic disorders even in nosological respects, and except in Ireland, where its history has been somewhat special, it might have been made the subject of a separate chapter in British epidemiology. But, for the same reason as in the cases of influenzas and epidemic agues and of scarlatina and diphtheria, it is necessary in a historical review to include infantile diarrhea, cholera nostras of adults and dysentery in one chapter, the reason being, that they are not clearly separated in the earlier records. So little are they separated in the London bills of mortality that the younger Heberden, in his fragment upon ‘The Increase and Decrease of Diseases,’ has understood the name of ‘*gripping in the guts*,’ under which enormous totals of deaths are entered in the bills for many years of the earlier period, to mean dysentery alone; having assigned that meaning to the name, and having observed, as every one must, the very palpable fact that ‘gripping in the guts’ steadily declined in the Bills from the end of the seventeenth century until it had almost disappeared from them in his own time, he has elaborately proved from the figures that dysentery was at one time among the most important causes of death in London, that it declined in the most regular way, and at length became all but extinct. This illustration of the increase or decrease of diseases has seemed so apt, the statistical demonstration so complete, that it has become a favorite example of those broad contrasts between the public health of past and present times which are not less pleasing in rhetoric than they are on the whole true in fact. But it happens that the particular instance is wholly fallacious and erroneous. It was not dysentery that the article ‘Gripping in the Guts’ meant for the most part, it was infantile diarrhea; which has not only not ceased in

our own time, but is commonly believed to be distinctively a product of the industrial town life of the present age. I shall show that it was one of the most important causes of London mortality from the Restoration onwards, and that although it is still one of the great causes of death in infants, yet that it had weekly mortalities in some of the hot summers of former times which were far higher in ratio of the numbers living than the diarrheal death rates of our own time. So far as concerns dysentery itself, it is indeed now rare in England and Scotland, and not common in Ireland; but the real history of its decrease has been altogether different, both in the period of it and in the extent of it, from what Heberden supposed. There are two reasons for the fallacy and error of that writer; the first, that he overlooked the question of age incidence in 'gripping in the guts'; the second, that he failed to observe that enormous annual totals of deaths under that head had been gradually transferred in the bills of the Parish Clerks to the head of 'convulsions,' until there were only a few of the old name left."

Creighton has given an interesting report on the summer diarrheas of infants in London during the seventeenth century and since. Sydenham, whose work on epidemic constitutions in London covers 25 years from 1661 to 1686, does not speak especially about infantile diarrhea, but, incidentally he does say that diarrhea is as natural to infants as salivation to adults, and adds that many thousands of infants are sacrificed by the imprudent efforts of nurses to check the diarrheas. He was also evidently conscious of the fact that choleraic diseases were at that time most fatal in the hottest months, for he says that the cholera morbus of August differs *toto caelo* from the disease with the same symptoms at other times of the year. Willis recognized the fact that the convulsions which often accompany teething were due in large part to intestinal disturbances. He wrote:

"As often as the cause of the convulsive distemper seems to be in the viscera, either worms or sharp humors, stirring up to torments of the belly, are understood to be at fault."

Morton's writings are equally unsatisfactory when we seek for information concerning infantile diarrhea. The fact that these great writers of the seventeenth and early part of the eighteenth centuries do not dwell more specifically upon infantile diarrhea calls forth the following comment from Creighton:

"It should be kept in mind, however, that it was from the populous liberties and outparishes occupied by the working class,—from Cripplegate, Shoreditch, Spitalfields, Whitechapel, St. Olave's, Southwark, Newington and Lambeth,—that the largest totals in the bills came. Sydenham in Pall Mall, Willis in St. Martin's Lane, and Morton in Newgate Street, were not likely to see much of the maladies of the poorest class, least of all the infantile part of these; and the fact that their illustrative cases of choleraic disease are mostly of adults should not mean that the age of infancy did not then furnish most of the deaths, as it certainly did in later times."

Fortunately, Harris in 1689 wrote a book on the acute diseases of infancy, and, that he was dealing with a disease which in this chapter we are calling cholera infantum, is shown by the following quotation:

“From the middle of July to the middle of September these epidemic gripes of infants are so common (being the annual heat of the season doth entirely exhaust their strength) that more infants, affected with these, do die in one month than in other three that are gentle.”

Creighton shows quite conclusively that in the earliest mortality statistics in London infantile diarrhea was generally reported under the name of griping in the guts; that during the latter part of the seventeenth century and first part of the eighteenth this designation was gradually changed from griping in the guts to convulsions, the latter term having quite completely supplanted the former by the year 1728. Creighton says:

“After that year (1728) it is obvious that any excessive mortality of the six or eight hot weeks of late summer or autumn corresponds to a great increase of the deaths under two years, which is also the increase of deaths from convulsions. But those were the ‘convulsions’ of a particular season, occupying exactly the place which ‘griping in the guts’ held in the weekly bills of certain years in the earlier period. As most of the deaths from infantile diarrhea are really from convulsions, it is easy to see that high weekly totals of deaths under that generic name must have been from infantile diarrhea—when they began to rise in August far above the ordinary level of convulsions to fall to the level again in October. It is by precisely the same reading between the lines that we discover, under the head of ‘diarrhea and dysentery’ in the modern registration returns, that there is hardly any fatal dysentery, not much fatal diarrhea of adults, but an erroneous fatality from the diarrhea of infants, especially in summer.”

During the hot weeks of certain years during the eighteenth century the total deaths in London were nearly twice the total births, and about half these deaths were in children under two years of age and were reported as due to convulsions or griping in the guts. Much the same condition prevailed in London during the nineteenth century, as is shown in Table V taken from Creighton.

TABLE V

MORTALITY FROM DIARRHEAL DISEASES PER 1,000,000 LIVING AT THE AGE PERIODS

	ALL AGES	0-5	5-10
1851-60	1080	5263	229
1861-70	1076	5985	160
1871-80	935	5728	69

Creighton points out that during the seventeenth and eighteenth centuries London was the only great urban community in the Kingdom and that it was far more urban in a bad sense then than it is now. He says:

“The houses stood closer together, many of them back to back in courts and alleys. The streets were narrower. The inhabited area had few or no open spaces besides the bed of the Thames. Not only the city and Liberties, but also the outparishes, were compact, as if within a ring fence, joining on to the open country abruptly, and not as now in straggling suburbs. It was hardly possible to take children out for an

airing, except in the West End. When Lettsom about 1770 applied the fresh air treatment to convalescent cases of typhus, he had to send the patients to loiter on the bridges spanning the Thames. As Cobbett said, London was a 'great wen,' in the correct sense of a shut sac which grew by distention. The soil was full of organic impurities, including the decompositions of many generations of the dead. A hot summer in former times raised effluvia from the ground such as the modern residents have no experience of. The life indoors was equally adverse to infants. Fustiness was favored by the window tax; a tenement house was apt to be pervaded by the excremental effluvia from the vault at the bottom of the stair. The worst time of all in London was the great drunken period from about 1720 onwards. Doubtless drink was then used, as it is sometimes now, to drug the fretful infants into torpor; but it told also upon them indirectly, inasmuch as dissolute parents would have bred children with *mala stamina vitae*. In all these respects there has been so great an improvement in London that, although its population now (1894) exceeds four millions, its death rate from infantile diarrhea, a distinctively urban disease, exceeds only by a little the mean of all England and Wales."

In recent years the death rates under one year of age per 100,000 births is greater in certain manufacturing cities in England, such as Liverpool, Manchester, and Preston than it is in London. It is worthy of remark that the death rate from all causes is highest in those cities showing the highest death rates under one year of age. This we deem a most positive negative answer to those who claim that the diseases of infancy and childhood weed out the unfit and thus benefit the race. Ballard has shown that of 332 infants dying of diarrhea in Leicester in 1881 and 1882, 141, or 42.5 per cent, were healthy, and 191, or 57.5 per cent, were weakly, thus showing that infantile diarrhea makes but little discrimination between the fit and the unfit. As we shall attempt to show later, infantile diarrhea is essentially a form of food poisoning and the effects of these poisons are not determined by the fitness or unfitness of the infant to live, but rather upon the amount of the poison administered in the form of food and the frequency of its administration. It is only fair to say that Creighton does not agree on this point with Ballard or ourselves and thinks that poor stamina, as he calls it, is a powerful factor in influencing the death rate from infantile diarrhea. He states that if the terms "healthy" and "weakly" were as determinate as bushels of grain, there would be more fitness in this resort to numerical precision. We might reply by saying that his estimate of "stamina" is quite as indeterminable as is our measure for healthy.

All through English statistics and epidemiologic reports from the beginning of the sixteenth century to the present, it appears that unusually hot seasons have been marked by undue prevalence and a high death rate among infants under two years of age. The years 1539 and 1540 were known all over Europe for the exceedingly high temperature of the summer months and for the great prevalence of choleraic diseases, especially among children. Sydenham regarded the seasonal increase

of cholera morbus, under which he classed diarrhea in both infants and adults, as coming on with the same regularity as the swallow in spring or the cuckoo in summer. It is undoubtedly true that the high death rates during the hot years were not wholly due to the increased prevalence of cholera infantum, but were in part augmented by cholera nostras in adults. Willis, writing of the London cholera in 1669-1670, says:

"I knew a great many that, though the day before they were well enough and very hearty, yet within 12 hours were so miserably cast down by the tyranny of this disease that they seemed ready to expire, in that their pulse was weak and slender, a cold sweat came upon them and their breath was short and gasping; and indeed many of them, that wanted either fit remedies or the help of physicians, died quickly of it. This distemper raged for a whole month, but began to decrease about the middle of October and before the first of November was almost quite gone."

When Asiatic cholera first appeared in England in 1831 there was much discussion as to whether it was the foreign disease or the recurrence of the virulent cholera morbus which the records showed had raged with great virulence during unusually hot seasons as far back as three centuries. Subsequent events, however, demonstrated that Asiatic cholera differs etiologically and epidemiologically from both cholera morbus and cholera infantum.

In 1825 Condie wrote rather extensively upon cholera infantum, but he devoted himself largely to symptomatology, pathology, and treatment. In discussing diet, he states that when cow's milk is used it should be perfectly fresh and should always be boiled. It appears from this that the employment of sterilized milk in cholera infantum is by no means confined to recent years. It is worthy of note that Condie and many other early writers on this disease called attention to the fact that children suffering from it, and especially during recovery, eat with great eagerness, and without apparent harm, salted fish.

Potter (1833) states that cholera infantum was unknown among the aborigines in this country and that it did not appear among the European settlers until the Atlantic cities had grown to be quite large. This author, like most others, places great stress upon the etiologic importance of temperature. He writes as follows:

"If we analyze all the circumstances under which the disease is gradually evolved, in the infantile system, and duly estimate their influence, it cannot be very difficult to find a rationale of the whole process of causation. What palpable cause can be assigned in early summer so obvious as the overwhelming influence of a *high temperature*, upon the exquisitely sensitive nervous system of children? It is scarcely possible to resist the conclusion that the matter of heat gives the first impulse, and that it originates a peculiar train of symptoms, in the relative condition of infancy and childhood, for which no other cause can account. Unless we

are deceived, we must allow a much greater latitude to this all pervading element, which will be found to exert a powerful influence on animate matter. In its action on the sentient system, it seems to be demonstrated, that it constitutes the first link in the chain of causation of a distinct genus of diseases, if it be possible to arrange them into several species, according to the organisms involved. If we were to attempt to frame a synoptical table of diseases, it would be impossible to resist the evidences of the power of heat in originating a genus peculiar to itself. Without such an active principle, both the varieties of cholera, some of those of dysentery, summer diarrhea, many cases of chronic hepatitis, as well as functional irregularities of the liver, would be anomalies in nosology."

Potter calls attention to the fact that a fall in temperature of from four to five degrees after a rain has a salutary effect on children sick at the time, reviving them in a most marked manner. In Baltimore he found most cases of cholera infantum in July. He held that the prevalence of the disease was modified by the cooler nights of August and gradually eliminated with the approach of autumn. He dwells upon the desirability of breast feeding and suggests that the best of cow's milk is not a fit substitute for that of the mother. He recommends that children be sent to the country with the coming on of hot weather as a preventive measure and he advises that deeply shaded locations be selected. In his practice he found that localities which had been stripped of their forests ceased to be proper places for summer resorts for children. He wrote:

"A hut, surrounded by woods, with only a yard and kitchen garden, is the most eligible spot that can be selected as an asylum against the disease, although there are many small settlements, only occupied a few years, that serve as a sufficient protection."

Some of Potter's remarks concerning the general hygienic care of infants are quite up to date. He recommends that during hot weather children should not be clothed too heavily, that they should have daily cold baths, and that no mother should fail to be informed concerning the dangers of artificial feeding. He recommends that children should not be weaned between the months of May and October, and states that nine-tenths of those who are deprived of the breast in June and July suffer from cholera infantum. He does not fail to dwell upon the importance of the food selected by the mother.

Lindsly (1839) reported on cholera infantum as seen in Washington, stating that one-half the total deaths in that city, and in some years more than one-half, occurred in July and August and were in children under two years of age. The chief cause of these deaths was cholera infantum, or, as it was locally designated, summer complaint. He attributed the chief cause to high temperature, recognizing that improper food and dentition increase the fatality. Around Washington at that time it was

difficult to find country refuges from this disease, on account of the wide prevalence of malaria.

Stewart condemned feather beds and heavy bedclothing and recommended hard mattresses with light covering. He also emphasized the fact that infants often get thirsty and appreciate cool water, especially on hot nights, and that every demand for drink does not mean that milk or other food is wanted. In regard to the cause, Stewart wrote:

“It is a remarkable fact in the history of this disease, that three circumstances are necessary to its production. The state of the system occurring during dentition, a high atmospheric temperature, and an impure state of the air; no one of these alone is in general sufficient to form it; nor do any two of them appear to be the agents of its formation. It never appears in the pure air of the country; nor does it prevail in cities at any other season than the summer; nor does it attack children, except during the period of dentition; scarcely ever occurring after the teeth have all appeared. To this last rule there have been a few exceptions; and the disease is then always attributable to some error in diet, by which the development of the follicular apparatus takes place prematurely, placing the child in the same pathological condition as that which occurs during the time of dentition, from a natural, though at times an excessive development of the mucous follicles of the intestines; a state which we have already seen to be the morbid condition of the bowels in this disease.”

It will be noticed from this quotation that Stewart did not place great stress upon artificial feeding. In this respect he differed from most of his contemporaries. He overemphasized dentition and it was pointed out by others that children teethe in winter but do not have cholera infantum in the cold months.

The year 1872 was in Philadelphia the hottest on record up to that time. The average temperature during July from 7 A.M. to 9 P.M. was 81.11°, while that for August was only a fraction below 80°. The summer was not only hot, but it was unusually wet. The rainfall during the three summer months amounted to nearly eighteen and one-half inches and during July and August there were 30 days on which rain fell. It is said that subtropical birds, which had never been seen north of the shores of the Gulf of Mexico, invaded the city. The weekly mortality ran as high as 855, equivalent to an annual mortality of 63 to the thousand. Cholera infantum was accredited with 1,666 deaths, nearly twice the number caused by this disease in the preceding summer. Besides, about 1,000 cases were attributed to the wasting diseases of infancy and 638 to convulsions. It is more than probable that large proportions of these were in reality due to infantile diarrhea. The total deaths of infants under one year of age for the year 1872 in Philadelphia numbered 5,862, while those for children under five amounted to 9,154. An interesting report concerning the meteorologic

and hygienic conditions in Philadelphia for 1872 has been made by Lee, Hamilton, Atkinson and Cohen.

According to Webster, cholera infantum caused about fifteen per cent of the infantile mortality in Massachusetts during the six years from 1865 to 1870 and 22.18 per cent of the deaths in Boston in 1870. In Massachusetts at that time, 84 per cent of the deaths from cholera infantum, 57 per cent of those from diarrhea, and 76 per cent of those from dysentery, occurred, during the third quarter of the year, with a mean temperature of about 67°. The following sentence from Webster's report is of interest:

"If we arrange the counties of Massachusetts in the order of *infant* and of *general mortality*, for 1870, the two lists are identical with the single exception of Nantucket where the former is very low and the latter high, from well known causes."

This is still another illustration of the statement that we have repeatedly made that in localities where the infant mortality is high, the general mortality is also high. People who do not take care of their children, as a rule have not reached that grade of intellectuality which is essential before a community knows how to take care of itself and realizes that health is the best asset any community can have.

In the early seventies, Webster found the highest infant mortality in Boston among immigrants. The worst immigrant sections compared with the best American districts showed an infant mortality of five to one. Ignorance, high birth rate and high infant mortality are frequently associated, and are in fact intimately connected, constituting a vicious circle.

The Fiske prize of the Rhode Island Medical Society was awarded to King in 1837 for a dissertation on cholera infantum. There is nothing of importance in this contribution; indeed, it is hardly up to the average of contributions to this subject of about the same date. King believed that cholera infantum is due to a specific miasm and when he attempts to explain what he means by this term he becomes hopelessly involved.

Grant, in his description of the insanitary condition of Memphis in 1852, gives a realistic picture that probably would have been applicable to many other small American cities of that time. Dogs and hogs were the only city scavengers. In 1852 the population of Memphis did not exceed 10,000 and 8.20 per cent of these died during the year; nearly one in every twelve, or a death rate of 82 per 1,000. More than one-third of all the deaths were in children under five years of age and Grant states that at that time Memphis had been stigmatized as the graveyard of children.

Writing in 1820 of cholera infantum in Philadelphia, Meigs says:

"In our mortality bill, for 1818, I find the record of 173 cases of cholera infantum; of these, 105 died under one year; between one and two years, 68. The whole number of deaths in children under two years of age, in all diseases and accidents, with the exception of still born, was 668. This statement leaves a proportion of one in four nearly, of deaths from cholera infantum. In 1819, we lost 1,185 children under two years of age. If we leave out 145 still born, we have 1,040 for disease and accidents; 225 children, under two years, died of cholera, so that in that year, not quite one in four died of the disease. I presume, that if all the cases which are truly dependent on, or connected intimately with our disease, were reported, we should have a mortality from it alone, of nearly one for every three cases. This is enough to establish, at least, the high importance of the affection, and, in view of the above circumstances, the strongest interest must be excited to investigate its history and treatment."

The ideas of Meigs concerning the etiology of cholera infantum at that time were very hazy. He wrote:

"From what I have said, it will be understood that I wish to maintain that cholera infantum depends principally on a loss of a healthy function of the liver, and that most of the collateral symptoms may be traced to the pervading influence exercised by that, over the other important organs of the body; that it consists, not in an organic change in the structure of the organ, but probably in a congested state of the whole system of the vena portae."

Artificial Feeding and Cholera Infantum.—As we have already observed, it was long ago noticed that the infantile diarrheas are largely confined to children who are artificially fed. This has been so evident, that for the past 100 years or more intelligent physicians have advised mothers that failure to breast feed their children multiplies many times the danger and the probability of the children dying before they reach two years of age. Furthermore, these same physicians advised mothers against weaning children between the months of May and October. Since cholera infantum is almost exclusively confined to the artificially fed and since the bulk of the food in artificial feeding consists of cow's milk, there must be some relation between cow's milk and the prevalence of the disease. It seems that man went along, certainly up to the early part of the nineteenth century, without being conscious of the possibility that cow's milk might become poisonous, especially to infants. As the settlement, development, and concentration in cities in this country proceeded, the infantile death rate increased. Having fixed his attention upon cow's milk as a possible factor in the causation of this disease, the medical man soon learned that as our cities grew and the time between drawing the milk and its consumption by the child grew longer, cholera infantum became not only more prevalent, but more fatal. This observation was coupled with the further fact, which fairly obtruded itself on the medical mind for centuries, that in some essential way the development of infantile diarrhea is dependent upon temperature. It required,

therefore, no great wisdom to lead to the inquiry as to what effect increasing temperature and prolongation of the time between the milking and the consumption of the product could have upon the properties of the milk. It was observed that children on the dairy farm drank the milk with impunity but when children in the city, from 24 to 60 hours later, drank the same milk a considerable percentage of them developed infantile diarrhea and the death rate from this cause was high. Quite naturally, the first investigations of cow's milk, so far as it concerns infantile morbidity and mortality, were along chemical lines. These studies led to the enactment of laws bearing upon the chemical composition of milk sold in cities. Such milk must contain not less than $12\frac{1}{2}$ or 13 per cent of milk solids and not less than 3 or $3\frac{1}{2}$ per cent of butter fat. Skimmed milk, if sold at all, must be dispensed from cans plainly marked with the true nature of the contents. These regulations were not without good results. It was the custom in the seventies of the nineteenth century for the dairymen roundabout Philadelphia and in other cities to dilute the lacteal fluid with ten per cent of water, claiming, and honestly believing, that if consumed without dilution it would prove altogether too rich in fat for the good of the infant urban consumers. When this milk reached the central depot in the city the distributor often added another ten per cent of water and not infrequently the retail dealer still further diluted and reduced the food value of this, the sole article of diet for thousands of children. There can be no doubt that for many years these practices were in vogue among milk dealers in many of our larger cities and they were not altogether unknown among those who supplied this product to the inhabitants of smaller cities. In the seventies and eighties we frequently took milk directly from the cans of the traveling distributor and a sample from the table of the boarding-house in Ann Arbor and found from ten to twenty per cent more water in the milk from the boarding-house table than in that from the can of the vender.

The next trick tried by the milkman was the addition of chemical preservatives to his product. He desired to delay the souring of milk, which would be easily recognized by the consumer and probably lead to the transfer of trade. To meet this fraud, laws were enacted forbidding the addition of any preservative to milk. It may be remarked parenthetically that there were many law suits in which the question of the harmfulness of formaldehyd and other milk preservatives was discussed in the courts. Some of these questions were never scientifically settled. Writing in 1920, Park says:

"The addition of germicidal substances to milk is illegal in almost every community; yet it must be conceded that some of these in small amounts are probably

harmless, while others are distinctly poisonous. I have watched infants throughout a summer which were fed on one part of formaldehyd to 20,000 parts of milk, and did not observe that they suffered in the slightest. Kittens grew to adult size on such milk in perfect health, and their tissues when examined under the microscope appeared to be perfectly normal. The digestive enzymes have been found by investigation not to be interfered with by a moderate amount of several other antiseptics. In spite of the harmlessness of the addition of small amounts of formaldehyd or of certain other bactericidal substances, the practice is universally condemned because of the difficulty of controlling the amount and varieties used.'

Vaughan, writing on the use of food preservatives at the time (1905) when discussion of this subject was at its height, said:

"From experiments made in my laboratory, I can state that the addition of formaldehyd to milk in quantities varying from 1-25,000 to 1-50,000 retards the growth of the lactic acid bacillus and thus delays the souring of milk, while it has but little effect on the multiplication of colon and typhoid bacilli. The most ignorant mother knows enough not to give her babe sour milk, but even the most intelligent mother might give the formaldehyd milk, laden with its poison-producing bacteria, because, so far as she can judge by appearance and taste, it is all right. The man who adds formaldehyd to his milk takes down the danger signal but does not remove the danger. Is he a philanthropist or is he guilty of manslaughter when the child fed on this milk dies? In cases of this kind, it matters not whether the preservative is directly, and in and of itself, harmful to the human body or not, its use should be prohibited. I am by no means sure that formaldehyd in the quantities in which it is used in milk is, in and of itself, of great harm to the body of man, but I am convinced that its use in milk, especially that fed to infants, is very properly condemned by the laws of many states. * * * So-called preservatives that remove the danger signal and leave the danger untouched should be condemned whether it can be shown that the substance employed is a poison or not. Even the most inert body belonging to this class should not be used, and certainly not in food fed to children, so large a proportion of whom die from milk poisoning."

Observation year by year has made it more certain that there is a direct relation between cow's milk used as a food and infantile diarrhea; that this relation is not determined by the chemical composition of the milk, i.e., by the proportion of carbohydrates, fats, and proteins, and that this relation is determined wholly by the bacterial content of the milk. If sterilized capillary tubes be passed into the thoroughly cleansed udders of healthy cows and milk collected in these, it will be found that such milk is sterile. This, however, is not true of milk as drawn from the udder even under the best practical conditions. Such milk always contains a few bacteria, mostly streptococci and staphylococci, for the most part in market milk eliminated by the growth of other microorganisms which find their way into milk from extraneous sources. Milk is a good culture medium for bacteria from manure, falling hairs, from epithelial scales rubbed from the udders of the cow by the hand of the milker, and for those which reach the milk through dust, dirt, and possibly other sources. After milk is drawn, both the kind and the number of

bacteria found in it will vary greatly with conditions, especially such as exposure to contamination and temperature.

The following procedures, more or less modified to suit conditions, are as a rule followed at present (1922) in all dairies supplying milk to cities: (1) Milch cows are not to be exposed to undue weather conditions and are not to be subjected to abuse of any kind. (2) The bodies of cows are cleaned daily, the hair about the udders is kept closely cropped, and the teats are wiped with a clean, damp cloth and dried before milking. (3) Decomposing food and refuse from manufacturing establishments are not to be fed to the cows and salt should always be within their reach. (4) The cows should have constant access to pure water. (5) The stables must be clean, well ventilated, and should provide for at least 500 cubic feet of air per animal. (6) The floors, walls, and ceilings of the stables should be tight, kept free from cobwebs and whitewashed at least twice a year. (7) Manure is removed daily from the stables. Lime is sprinkled daily on the floor and in the gutter. (8) When the milk is drawn from a cow it is immediately carried to the milk-house, strained through absorbent cotton, cooled, and kept at a temperature not above 50° F. The milk-house is screened and kept free from flies. (9) Milk pails are thoroughly washed or steamed before each milking. (10) The milker wears clean, white outer garments and washes and dries his hands before milking. (11) Cows are quietly and thoroughly milked at the same hour morning and evening and in the same order. (12) If any part of the milk is of unnatural appearance or if by accident dirt gets into the milk pail, the content of that pail is rejected. (13) Careful observation of the personnel of the dairy is made day by day and no person exposed to a contagious disease is permitted to milk. (14) Milk is shipped in refrigerator cars.

Four factors must above all others be kept in mind if a sanitary and satisfactory milk supply is to be produced—(1) the employment of a small-top milk pail, (2) sterile utensils, (3) clean cattle and stable and (4) the immediate cooling of the milk to below 60° F. and preferably below 50° F. The efforts of dairy inspection agencies should be largely confined to these four important factors.

In some dairies milking is done by machinery.

According to Park, the sale of the following grades of milk is permitted in New York City: Grade A raw milk or cream; this must come from herds which are tested annually with tuberculin and found free from tuberculosis. This grade of milk must contain not more than 60,000 bacteria per c.c. and the cream not more than 300,000 bacteria per c.c. at any time during transit or at the time of delivery. It must be delivered to the consumer within 36 hours after being drawn. Except

on a special permit, milk of this grade may be delivered only in bottles, the caps of which shall be marked with the words "Grade A Raw" in black and bear the name and address of the dealer.

Grade A pasteurized milk or cream; this grade may be sold only by dealers licensed by, and complying with the rules and regulations of the Board of Health. The tuberculin test is not required. This grade of milk shall not contain more than 30,000 bacteria per c.c. and the cream not more than 150,000. It shall be delivered within 36 hours after pasteurization. Except under a permit, this milk is sold only in bottles, the caps of which show the name of the dealer and the hour when it was pasteurized. This milk must, in pasteurization, be subjected to a temperature of 142°-145° F. for not less than 30 minutes.

Grade B pasteurized; this grade is sold only by licensed dealers complying with the regulations of the Board of Health. The tuberculin test is not required. This milk shall not contain more than 100,000 bacteria and the cream not more than 500,000 when delivered to the consumer or at any time after pasteurization. It must be delivered within from 36 to 48 hours after pasteurization. It may be handled and delivered either in bottles or in cans. The cans or bottles shall bear labels marked "Grade B" in green letters and give the hour of pasteurization and the name of the dealer. Milk and cream of this grade must be pasteurized at a temperature of from 142° to 145° F. for not less than 30 minutes.

Grade C pasteurized; this can be sold only by licensed dealers complying with the regulations of the Board of Health. The tuberculin test is not used. This grade of milk shall not contain more than 300,000 bacteria per c.c. and the cream not more than 1,500,000 after pasteurization. It must be delivered within 48 hours after pasteurization and is delivered in cans only. The tags on the cans are marked in red "for cooking only." The pasteurization of this milk is carried out at the same temperature and for the same time as in other grades.

Buttermilk, sour cream, sour milk, kumyss, etc., cannot be made from any milk of less than Grade B and must be pasteurized before being permitted to sour. It will be understood, of course, that the laws concerning the dilution of milk, the removal of fat, and the addition of preservatives, are still in force. In municipal laboratories close tab on the chemical composition and bacterial content of the products of all dealers, is kept.

In many localities two or more physicians, generally pediatricians, undertake, under the designation of a Milk Commission, to guarantee for certain dairymen that their product will be of the highest possible purity, both chemically and bacteriologically, and safe for infant feeding. This milk is sold under the name "certified milk," and is, barring

accident of contamination, a safe food. The commission formulates rules and regulations, which are similar to those we have already given, for the dairy, for the drawing, the cooling, and the shipping of the milk. The idea is that every step in the handling of milk should be attended with the utmost cleanliness. The cows are all tested with tuberculin and are examined at short intervals by competent veterinarians. Frequent inspections are directed to the personnel of the dairy farm and to the conditions under which the milk is protected from dilution, the addition of chemicals, the removal of cream, and the introduction of bacteria. The commission undertaking this work for one or more dairymen, reserves for itself the right to make inspection whenever it sees fit, without preliminary notification, and to impose upon the dairyman such rules and regulations as it deems wise, and to change these whenever it sees fit. The number of bacteria per c.c. in certified milk must not exceed 10,000 and in most cities it is provided that certified milk shall at no time after the preliminary cooling reach a higher temperature than 45° F. and should reach the consumer not later than 36 hours after its production. Many years ago Goler, health officer of Rochester, N. Y., demonstrated that both morbidity and mortality among infants can be greatly decreased simply by due attention to cleanliness at every step in the care of the milk from the cow to the baby consumer. It will be understood that accidents may happen to certified milk, but, when all rules and regulations are properly carried out, this is a safe infant food. Quite naturally, the cost of certified milk is greater than that supplied to the people at large. The idea of furnishing certified milk apparently originated with Coit, of Newark, N. J., who put his plan into operation in 1893. The purposes of Coit were (1) to secure a milk free from pathogenic bacteria; (2) to so handle the milk that saprophytic bacteria would not multiply in it or do so very slowly; (3) to secure a milk which should not be deficient in any normal constituent, such as carbohydrate, fat, and protein. The number of children reared on certified milk is small.

Insofar as local conditions will permit, the complicated grading of a milk supply should be avoided. The municipality with an ideal supply would be one which has only one grade of milk, produced on farms where the sanitary conditions are maintained at the best, through rigid inspection, and where all milk before delivery to the consumer is pasteurized, as a safeguard against accidental infection.

Many of our large cities have only two or three grades of milk. In Detroit there are three grades—first, certified milk; second, Class “A” milk, and third, market milk. Milk of the first two classes is not pasteurized and constitutes only 1 per cent of the total milk supply of the city. The certified milk is that which is produced under the rules and regula-

tions of the County Medical Milk Commission, while Class "A" milk is produced on farms of the highest sanitary rating, where all animals have been given the tuberculin test. It is believed that this class of milk will eventually be pasteurized. The market milk, which constitutes 99 per cent of the city's supply, must be produced in accordance with the following regulations:

First—That the pasteurization of the milk should be performed by a process whereby every portion of the milk is raised to a temperature of 145° F., and retained at that temperature for a period of thirty minutes by the holding process, and no other process should be adopted or used. Immediately thereafter the milk must be cooled below a temperature of 50° F.

Second—That no pasteurizing equipment should be used that has not been approved by the Health Department.

Third—That each pasteurizing apparatus should be equipped with a time and temperature recording apparatus kept under lock and key, and that records should be filed with the Health Department on Thursday of each week.

Fourth—That all pasteurized milk should be plainly marked on each bottle cap or other container in which such milk is delivered to consumers, with the label bearing the inscription "pasteurized milk" together with the day of the week on which said milk has been pasteurized. Each pasteurizing plant is given a number, and this number must appear on the cap or top of the container.

Fifth—That pasteurized milk should contain not more than 100,000 colonies of nonpathogenic bacteria per c.c. in samples taken from containers being delivered to consumers.

Sixth—That immediately after the process of pasteurizing and cooling, the milk must be put into the final container, unless it has been pasteurized in the container in which it is to be delivered. The last mentioned container must be sealed.

Seventh—That milk should not be pasteurized more than once.

Eighth—That pasteurized milk should be delivered to the consumer not later than twenty-four hours after pasteurization.

Ninth—That all cream and skim milk should be pasteurized or made from pasteurized milk.

Tenth—That buttermilk should be made from milk or cream pasteurized before churning.

When medical men first began to realize the harm being done to the infants under their charge by the bacteria in milk, they resorted to sterilization. This was nothing more than the application of the advice given quite a hundred years ago, that when children must be artificially

fed, fresh cow's milk should be used and it should always be boiled. The use of sterilized milk was not altogether satisfactory, although undoubtedly it resulted in the saving of many lives. Cases of scurvy began to develop and the profession came to realize that in the process of boiling some injury is done to the food value of the milk. This led to the substitution of pasteurization for sterilization. Objections have been raised to pasteurization. It has been argued that the dairyman, knowing his product is to be submitted to this process, is likely, unless closely watched, to relax somewhat in the principles of cleanliness. It should be clearly understood that a dirty milk or one containing a large amount of bacteria can never be converted into the best kind of infant food by any process. Cleanliness is a necessary prelude to both sterilization and pasteurization, provided the product is to be of the best possible quality. Even dead bacteria, if present in milk in large quantities, may be harmful to the child. All bacterial poisons are not destroyed at the boiling point and all bacteria contain poisons. In the pasteurization of milk, the best results are obtained by heating in a closed vessel at a temperature of not less than 142° F. for 30 minutes, and it should be plainly understood that this exposure to heat does not completely sterilize the fluid. It is essential that after pasteurization the milk that is to be fed to the infant must be kept at a low temperature, preferably not above 45° F., and certainly not above 50° F. The effect of temperature upon the destruction of bacteria in milk depends upon the kind of bacteria present and, in part, upon the number; for instance, tubercle bacilli in milk are killed after an exposure of one minute at 176° , while 30 minutes are required to accomplish the same purpose when the temperature is 142° . Powdered milk is coming more largely into use, but the experience with it as an infant food has not been sufficiently large to justify positive conclusions. It may be made, and generally is, from skimmed milk and this necessitates the addition of fat when the powder is dissolved.

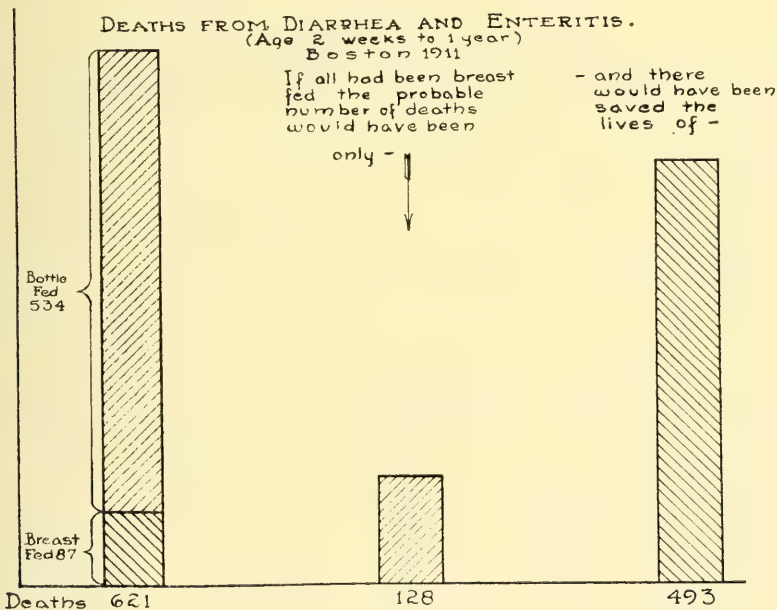
As we have already stated, much more work has been done on the bacteriology of milk with the special purpose of ascertaining what, if any, species of bacteria is concerned in the causation of infantile diarrhea. Since no positive result has been obtained in these efforts, we would not be justified in going into detail concerning the kinds of bacteria found in milk. Search has been made for specific organisms in the milk fed to children when cholera infantum develops, in the stools of such children, and in their bodies after death, but no one has been able to even throw a suspicion upon any one species of bacteria as the specific cause of cholera infantum. Recently (1920) Park wrote:

"After two years of effort to discover some relation between special varieties of bacteria found in milk, and the health of children, the conclusion has been

reached that neither through animal tests nor the isolation from the milk of sick infants have we been able to establish such a relation. Pasteurized or sterilized milk is rarely kept longer than 36 hours, so that varieties of bacteria which after long standing develop in such milk do not enter into the problem. The harmlessness of cultures given to healthy young kittens does not of course prove that they would be equally harmless in infants. Even if harmless in robust infants, they might be injurious when summer heat and previous disease had lowered the resistant and the digestive power of the subjects."

According to Park, nearly eighty per cent of infants during the first nine months of life in New York City receive nourishment entirely or chiefly from the breast. It follows, therefore, that artificial feeding can

ONE REASON FOR BREAST FEEDING.



Davis, A. J. P. H. Vol. II, 1912, Pg. 67.

Fig. 6.

affect only about twenty per cent of infants in that city under nine months of age, and it is during this period in which most deaths occur from intestinal diseases. Cronin, as quoted by Park, has tabulated 1,000 consecutive deaths from enteritis under two years of age and has found that eighty-one per cent of these were under nine months, thirteen per cent during the next three months, and only six per cent in the second year. The importance of cow's milk in infant feeding is brought out by the fact that, although more than seventy-five per cent of infants are nourished from the mother's breast, seventy-eight per cent of the 1,000 cases tabulated, as stated, dying from enteritis, were fed on cow's milk or patent foods.

Park has tabulated his observations on infantile diarrheas according to season and the kind of milk employed. He has divided the results of these observations into the following groups: (1) Those infants who during the period covered have gained normally in weight and have had no appreciable diarrhea. (2) Those who have gained but slightly in weight or have remained stationary in this particular and in whom temporary and slight diarrhea has shown itself. (3) Those in whom there has been a marked loss in weight with considerable diarrhea. (4) Fatal cases. These observations are tabulated, as follows, according to the kind of food and the season of the year.

TABLE VI
FOOD AND RESULTS.—WINTER

	DID WELL	DID FAIRLY	DID BADLY	DIED	TOTALS
Store milk	47	6	2	0	55
Condensed milk	39	5	2	2	48
Good bottled milk	51	13	1	3	68
Milk from Central Distributing Stations	35	20	4	0	59
Best bottled milk	5	9	1	0	6
Breast feeding	7	1	0	1	9
Totals excluding cases counted twice	156	41	8	6	211

TABLE VII
FOOD AND RESULTS.—SUMMER

	DID WELL	DID FAIRLY	DID BADLY	DIED	TOTALS
Store milk	21	23	20	15	79
Condensed milk	22	20	14	14	70
Good bottled milk	37	23	29	9	98
Milk from Central Distributing Stations	84	33	24	4	145
Best bottled milk	9	3	0	0	12
Breast feeding	17	7	7	0	31
Totals, excluding cases counted twice	184	108	88	41	421

Grouping these results, we note the following percentages of babies that "did well" or "fairly": Store milk 56 per cent, condensed milk 60 per cent, good bottled milk 51 per cent, Central Distributing Station milk 81 per cent, best bottled milk 100 per cent, breast feeding 77 per cent. The results are clearly in favor of the better grades of milk and breast feeding.

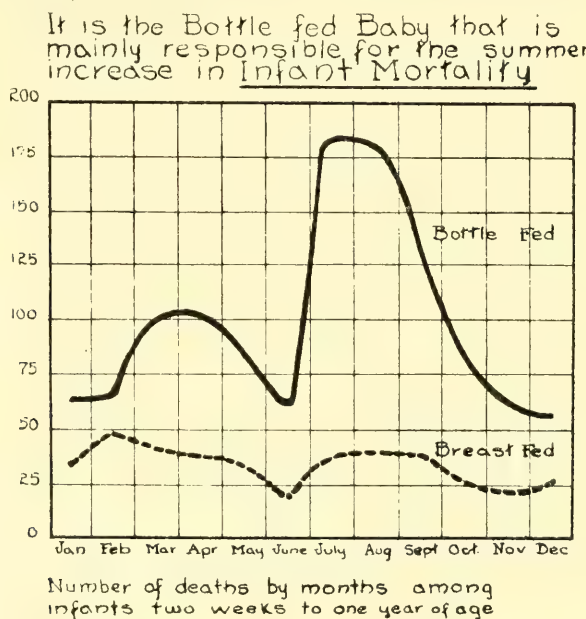
As emphasized by Park, much depends upon the intelligence of the mother, her capability, and willingness to carry out directions as to the kind of milk selected, the quantity to be given, and the frequency of feeding. The purest milk placed in the hands of an ignorant or careless mother may within a few hours become a deadly poison to her child.

Printed directions, so far as the ignorant mother is concerned, are of but little value. In the first place, many of these people cannot read and many of those who can, fail to understand. It results from this that among the tenement-house dwellers better results are secured when the mother carries her child daily to some central station where the supply for the next 24 hours is prepared and placed in her hands, with such explicit directions that she can scarcely fail to carry them out. While there is some exaggeration, there is much more truth, in the broad statement that whether a child lives through its first two years or not is largely determined by the intelligence of the one who feeds it, and generally this is the mother.

We may ask whether the poison which acts upon the child comes from the milk, from the bacteria contained therein, or from products which result from the action of the bacteria on the milk. This question cannot at present be definitely answered. We are inclined to the opinion that if absolutely pure milk is absorbed from the alimentary canal without previous digestion it may cause illness and possibly death.

Pryer has shown that one gram of casein contains enough protein poison to kill 800 guinea pigs when injected intravenously. That milk is sometimes absorbed unchanged has been shown by its detection in the circulating blood of infants by the sensitization test. It has not been demonstrated, however, experimentally that the protein poison in this absorbed milk is liberated. Bacterial proteins contain much less of the protein poison than is found in casein; in fact, about ninety per cent of casein consists of the protein poison, while only from thirty to forty per cent has been obtained from bacterial proteins. If poisons be formed by the action of the bacteria on the milk constituents, these might be absorbed and would practically lead to the same result as would follow or might follow the absorption of unchanged milk or slightly changed bacterial proteins. It has been shown experimentally that milk is more readily absorbed unchanged from the intestines of young rabbits than from adults of the same species. While this matter is not open for experimental demonstration in infants and while reasoning by analogy is always dangerous, there is good reason for believing that proteins, especially milk and bacterial proteins, are absorbed more readily from the intestinal tract of infants than from that of adults. At the same time, it is an incontrovertible fact that cholera infantum occurs in children so rarely after they have passed the second birthday that it is no great exaggeration to say it does not occur. Older children and adults may take with impunity milk so badly contaminated bacterially that its administration would be almost certainly productive of symptoms, at least in an infant under nine months of age. It must be clearly under-

stood that, while casein contains a large amount of the protein poison—a larger amount by far than has been found in any other protein—still all proteins contain this poison. It appears to be quite conclusively demonstrated that when a choleraic diarrhea develops in an infant the proper thing to do is to stop immediately the further administration of milk, good or bad, for a few hours at least. When a child is having its food partly from the mother's breast and partly from cow's milk, milk from both sources should be temporarily withheld. Possibly failure to do this is in part responsible for the comparatively high death rate among



Experience in Boston, 1911. Described by Davis A & DH Vol II, 1912. Page 67

Fig. 7.

infants receiving their food from these two sources. It has been observed that deaths among such infants do not, at all times at least, differ materially from the rate occurring among those who are fed exclusively on cow's milk.

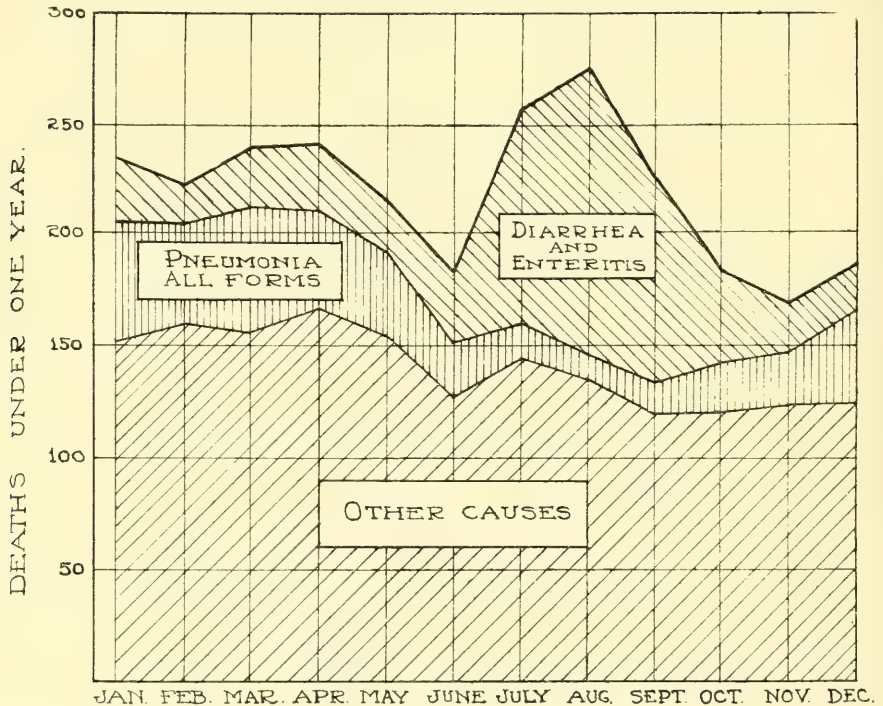
Seasonal Influence.—We have repeatedly stated that cholera infantum and kindred diseases are practically confined to the hot months and that their prevalence increases directly as the mercury in the thermometer rises. This observation extends as far back in time as we have any record of infantile diarrhea, under whatever name it appeared. As illustrative of this fact, we reproduce herewith Table IX as given by Hirsch.

We have ascertained so far that cholera infantum and kindred diar-

TABLE IX
TABLE OF MORTALITY FROM CHOLERA INFANTUM ACCORDING TO MONTHS

	PERIOD	TOTAL												IN OTHER MONTHS
		DEATHS	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
Königsberg	1858-1862	638	17	23	22	26	46	95	97	150	80	36	23	23
Berlin	1877-1882	17641	161	135	217	283	713	4418	6226	2889	1612	634	200	153
Nürnberg	1861-1863	441	11	10	15	16	28	9	52	152	93	28	15	12
Stuttgart	1853-1862	516	5	7	8	18	18	37	102	170	82	40	18	10
Massachusetts	1871-1880	2118	2	3	4	8	15	95	720	770	370	95	19	10
Baltimore, Md.	1850	347	-	-	-	-	-	10	131	122	75	9	-	-
New York	1816-1826	1245								1215				30
New York	1837	253								226				27
Rhode Island	1864	890								855				35
St. Louis, Mo.	1843	488								325				163

rheal diseases are in some way influenced by the following factors: (1) The age of the child. (2) Its food. (3) The weather. This disease occurs only in infants under two years of age, only among those partly or wholly artificially fed, and only during the hot season. These factors must be interrelated. The infant under two years of age we may say, speaking broadly, is susceptible to this disease, while older children are immune. Even the infant may in the winter time take food without harm



SEASONAL INFLUENCE ON INFANT DEATHS

Average of years 1916, 1917 and 1921 for Detroit. Three intervening years omitted because of excessive deaths caused by Influenza Epidemics.

† Figures adjusted for months of 31 days. February deaths multiplied by $31/28.3$, April deaths by $31/30$ etc.

Fig. 8.

which would be harmful if taken in the summer time. The most reasonable supposition is that the child under two years of age owes its susceptibility to the greater readiness with which poisons are absorbed through its intestinal walls. The relation of the temperature to the other factors is more uncertain and more complicated. Other things being equal, the higher the temperature the more rapidly do bacteria multiply in the milk.

This is reflected in the monthly variation in the bacterial content of milk samples from dealers' wagons as reported from Detroit during 1921 and 1922.

MONTH	PER CENT SAMPLES
	UNDER 100,000 BACTERIA PER C.C.
June	58
July	38
Aug.	63
Sept.	73
Oct.	90
Nov.	91
Dec.	97
Jan.	92
Feb.	91
Mar.	89
Apr.	90
May	83

The more rapidly bacteria multiply the more labile are the proteins, both those in the bacteria and those in the milk. At present we determine the fitness of a milk for infant feeding by its bacterial content or by the number of bacteria per c.c. This is the best we can do. It is more than probable, however, that more important than the number of bacteria is the rate at which these are multiplying. Besides the effect of temperature on the growth of bacteria in the milk is the possible influence of temperature upon the digestive capacity of the child and the rate of absorption of poisons through the intestinal walls. Many are inclined to regard weather temperature as the primary factor in the causation of cholera infantum, but no one claims that high temperature alone causes the infantile diarrheas. When we have three essential factors in the production of any phenomena, it is perfectly proper to state their sequence and interrelation, and from this standpoint we are inclined to join those who believe that weather is the primary factor. The weather temperature increases the production of the poison and at the same time lowers the resistance of the child. In our opinion, the weather temperature with reference to this disease is only approximately registered by the thermometer at the Weather Bureau, or even that in the room, but is correctly determined only in the atmosphere immediately surrounding the little patient. Fortunately, this is more or less under the control of those in care of the child. The older observers of this disease were right when they recommended that feather beds, large pillows, and heavy woolen blankets should be discarded, certainly in hot weather. They were also right when they advised migration to the shades of the country in order to escape the greater light of the sun and the reflected heat of buildings and pavements. Cool and frequent baths, proper attention to dress, and frequent excursions into the open, were recommended

by our hard-headed ancestors of more than 100 years ago. Fortunately, new inventions have placed largely within our control the temperature of rooms, even for those who must remain in the city during the hot season. Screened windows admit fresh air and electric fans do much to mitigate the effects of the high temperatures of summer on the babies.

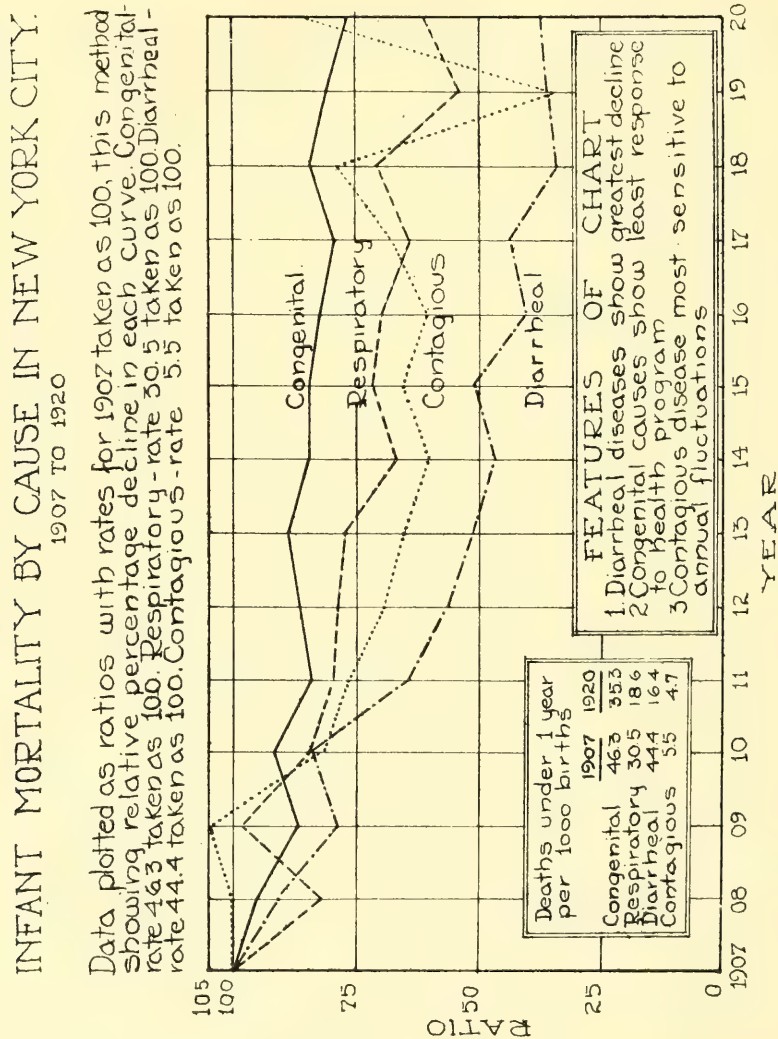


Fig. 9.

Recent Reduction.—The census figures concerning deaths from diarrhea and enteritis in infants under two years of age are not very illuminating. The rates given are per 100,000 population, while what we want to know is the rate for those of that age period. Different commu-

nities differ widely in the number of infants and rates for the total population may be highly misleading. However, it is a recognized fact that there has been a marked reduction in the infantile death rate all over the civilized world, and especially in this country, in the last twenty

DEATH RATE AMONG YOUNG CHILDREN IN NEW YORK CITY. 1907 TO 1920

Data plotted as ratio with rates for year 1907 taken as 100, this method showing relative percentage decline in each curve. Under 1-rate 144 taken as 100, 1 to 2-rate 53 taken as 100, 2, 3 and 4-rate 146 taken as 100.

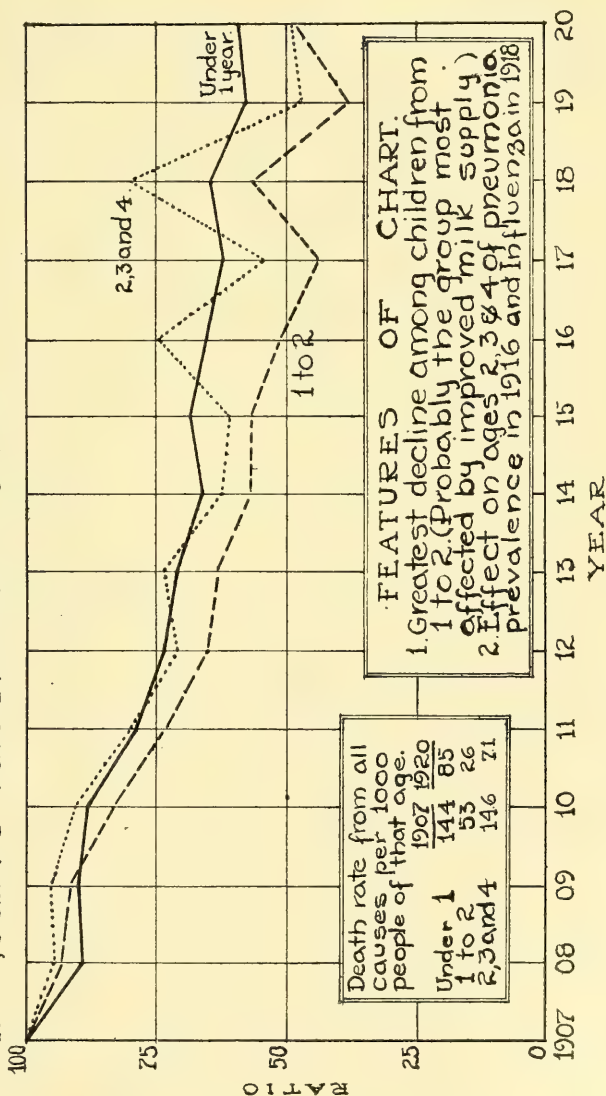


Fig. 10.

years. The census figures state that, in the registration area as a whole, the average death rate from these diseases from 1906 to 1910 was 96.2. Since that time there has been, on the whole, a fairly satisfactory decrease, with some fluctuations, according to the intensity of the heat of

summer, the figure in 1918 standing at 58.3. In 1918 the highest rates were in Maryland (115.8), Pennsylvania (95.7), North Carolina (81.0), New Jersey (77.0), and Massachusetts (75.7). The states showing low rates were Washington (13.9), Oregon (14.3), Minnesota (22.3), Utah (23.1), and Wisconsin (28.3).

Control.—Infants under nine months of age should be exclusively breast-fed unless the physical condition of the mother renders this impossible. As we were told by some of the older authors, weaning a child at the beginning of, or during, the hot season markedly endangers its life. When the child must be artificially fed, it should be plainly understood that the kind of milk chosen for it is of the utmost importance. Proprietary baby foods and condensed milk are least desirable, and, in fact, their employment is followed by the highest mortality. Milk selected as the food for the child should come from healthy animals kept in a dairy, supervised and regulated as we have elsewhere indicated. Either certified or the highest grade market milk should be selected. The milk should contain the food principles in proper proportion, should be free from any preservative, and should have as low a bacterial count as possible.

The number of mothers who breast feed their children varies greatly in different countries, in different communities in the same country, and among different classes in the same community. There can be no doubt that in this country among all classes and conditions breast feeding has become much more general in recent years. This is due largely to the persistence of physicians in emphasizing the fact that the child's life is greatly endangered when artificial feeding is resorted to. We are indebted to Bleyer, of St. Louis, for an illustration of what can be accomplished by public education in the advantages of breast feeding. He averaged the weights of babies brought to the Infant Welfare Stations, and observed that these weights are much closer to an average or normal weight in 1920 than in 1910. He likewise finds that breast feeding is far more common in 1920 than ten years previous. Thus, of the babies under three months of age, ninety-two per cent were breast-fed in 1920, whereas in 1910 but thirty-nine per cent were breast-fed. Without doubt, the increase in breast feeding has been the direct cause of the superior nourishment. There is no pediatrician in this country, so far as we know, who has not, both in his scientific and in his more popular writings upon infant welfare, stressed this point; indeed, the importance of maternal nursing has been so deeply impressed upon the public in general that the laws of more than one state say that every mother shall nurse her child for at least three months. This is a wise legal provision and, while there are certain exceptions that must be made, it necessitates

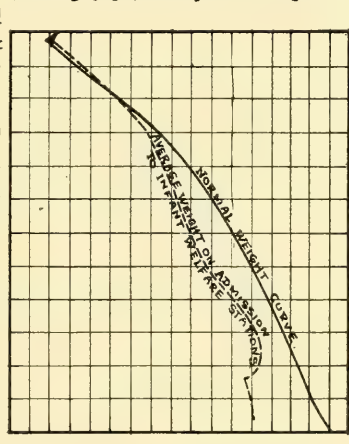
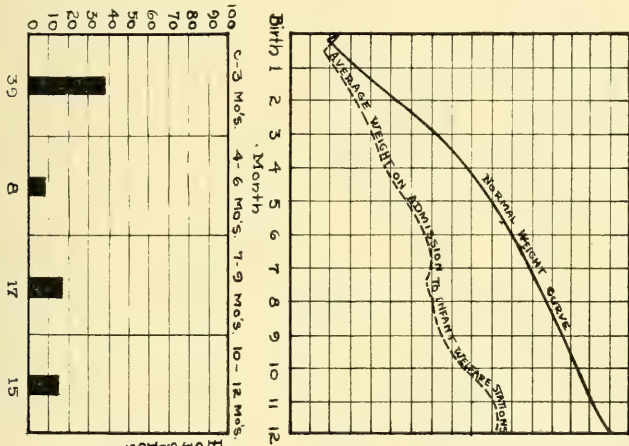
that some one should explain in every case in which the law is not complied with. Recognizing the fact that the mother should nurse the child makes it the more imperative that the mother, both before and after confinement, should be so favored that she is in the best possible condi-

•Some results of a 10 Year campaign for Breast Feeding in St. Louis.

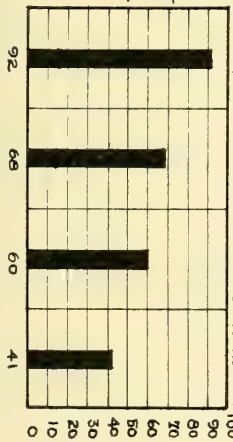
1910

Weight
in grams.

1920



Percentage
of Babies
Breast Fed
from
Infant
Stations.



Data from Dreyer Mother & Child Vol. 2, Nov. 1921
Page 496.

Fig. 11.

tion to supply her young with the proper food. This has led to additional legal enactments forbidding the employment in heavy work of women during the latter months of pregnancy and during the first few weeks after confinement. During these periods the mother must be relieved of every unnecessary stress and strain, not only for her own sake, but for the good of her child. Again, it can be shown that breast feeding is not

only the safest, but it is the cheapest, and the extra money which would need to be expended in securing a safe artificial food for the child is sufficient to place the mother under favorable conditions so that she may furnish the food her child demands. Breast feeding is not only good for the child, but it is also of benefit to the mother. The first nursings empty the breasts of the colostrum stored by nature for the benefit of the child, and at the same time it promotes the return of the uterus to a normal state. The child, except under most unusual conditions, should go to the breast four times on the first day after birth and about six times on the second day. In these first nursings the infant receives the food which Nature has been preparing for it during the nine months of its intra-uterine life.

While it is the rule that every mother should nurse her child for at least three months, there are exceptions in which it is well for the child and for the mother that this rule be broken. Most pediatricians think that the following conditions in the mother render her unfit to nurse the child and, moreover, that she cannot do so without injury to herself: (1) Tuberculosis, either latent or active, is believed to unfit the mother for nursing, inasmuch as it has been observed that the progress of the disease in her is hastened by the nursing. (2) The mother who has suffered during her pregnancy or at the time of confinement from eclampsia or puerperal septicemia or who has advanced nephritis should not nurse her child; indeed, children put to the breast when the mother is in one of these conditions have suffered seriously and some have died promptly. (3) There are certain chronic diseases, the seriousness of which may unfit the mother for the performance of this function. The late Professor Jacobi, who had large experience as a pediatrician, claimed that one hundred per cent of mothers can, at least temporarily, nurse their children. Possibly there is in this a slight exaggeration, but the exceptions are so few that the statement need not be challenged.

It follows that if the mother is to nurse the child, and she certainly should, except in the rarest instances, she must fit herself for this function. If a laboring woman, rest must be provided for her; if poor, proper food must be obtained for her; and we are glad to say that with the prenatal clinics, now well established in practically all our cities, no woman about to become a mother needs to starve or even to subsist on insufficient diet. If the mother be a society woman, she must, or should, for the time being, give up her social engagements and devote her life to her maternal functions. It goes without saying that if a mother is to supply her child with proper food she must feed herself properly and refrain from every act which would render her milk less suitable in supplying the demands of her offspring. Privations, exhaustive work, society dissi-

pations, may unfit the healthiest mother for elaborating food proper in kind and quantity for her child. The nursing of children, like every other normal function, should be performed with regularity. The progress of the babe when fed upon its mother's milk is easily determined by its general physical condition and by its rate of growth. It should be weighed at least once a week and if there be any doubt about its condition, twice a week or even daily. Regular feedings, at stated hours, are beneficial both to mother and child. It enables each to secure at least one period during the day covering several hours of uninterrupted rest. Slight and temporary digestive disturbances in the child should not lead to the hasty conclusion that the mother's milk is not suitable. There may be something wrong for the time being in the food of the mother, or some slight ailment which is disturbing her milk supply. As a rule, breast feeding on account of slight digestive disturbances should not be discontinued or replaced by artificial feeding without consultation with a pediatrician. Weaning the child, especially during the first six months of its life, is rather a serious matter and should not be resorted to without proper justification. There are, however, possible conditions which render weaning quite necessary and this may happen before the babe has reached six months. The most common of these conditions is intercurrent pregnancy. The coming child may rob its brother of its birthright in part. When the mother's milk is too scanty or inferior in quality and the child fails to grow normally, it is often the case that the mother's milk may be improved by alterations in her diet or by securing for her longer periods of rest; on the other hand, it sometimes happens that the mother in her anxiety to see her child grow rapidly, feeds herself unduly and produces an overrich milk. This is easily remedied by making proper changes in her diet.

Other things being equal, the child should be weaned at about the end of the ninth month, but the nursing time should be prolonged in case this date falls at the approach or in the period of hot weather. We have already emphasized the fact that the danger of weaning a child between May and October should always be considered with great care. Undue prolongation of the period of lactation is not good in most instances either for child or mother. The former ceases to grow, normally at least, and possibly loses something. The mother is carrying a burden a little heavier than she should bear. With baby clinics and milk depots so readily accessible it is well to consult the physician when weaning seems desirable.

Even the breast-fed child is not wholly immune to the distressing effects of hot weather, and whether a child be breast-fed or artificially fed, the ascent of the mercury in the thermometer should increase the

attention given to its welfare. In either case, hot weather lessens the digestive capacity of the infant and quite certainly increases the readiness with which undigested or partially digested food may be absorbed from the alimentary canal. As the days grow warmer and the intensity of the heat increases the child needs less food and more water. Besides this, the intelligent mother can do much by employing cool baths, lessening the weight of the clothing, drawing the shades, and possibly starting the fan in order to keep the temperature immediately about the babe somewhat in moderation.

Wet nursing has never been popular in any class in this country. In the first place, professional wet nurses, so well known in Europe, scarcely exist here. Most American mothers wish to nurse their own children and those who cannot do so prefer as next choice the feeding of the child. Then again, even the poor woman, for the most part at least, desires that her child should have the full supply and is not willing to have it divided with the child of another. Acute conditions, however, sometimes arise when a wet nurse is, at least temporarily, the best solution for a difficult situation. It goes without saying that she should be healthy and free from syphilis and tuberculosis. There is a popular prejudice that leads to the belief that mental and moral qualities, especially those which are undesirable, may be transmitted through the mother. Fortunately, the child neither in utero nor at the breast has its moral nature tinted with or determined by that of its mother or its foster mother.

The milk of each species of mammal is a secretion *sui generis* and peculiar to that species. Throughout the period of gestation the physiologic processes in the body of the mother are concerned, among other things, in preparing the sustenance of the child for a time after the anatomic separation from the mother takes place. At birth the child ceases to be anatomically a part of the mother, but under normal conditions it continues physiologically a part of the mother. The food and tissues of the mother are utilized in the preparation of the food for the young. In mammals, nature provides for the continued feeding of the young through the tissues of the mother for a time after birth. The mother who cannot nurse her child, for at least a time after its birth, interrupts prematurely the physiologic relation that normally exists between her and her child. The milk of no other mammal can adequately supply the loss to the child which follows the failure of the mother to nurse it. Both mother and physician should thoroughly appreciate the importance of maternal nursing to the welfare of the child, and it should be deprived of its physiologic food supply in case of necessity only.

When artificial feeding must be adopted the milk of the cow is practically the only available source of food supply for the infant. Cow's

milk cannot be made into woman's milk by any physical, chemical, or biologic manipulation. At best it must be regarded as a substitute resorted to in case of necessity only. While cow's milk cannot be converted into woman's milk and while its use in infant feeding should always be regarded as undesirable, much can be done in the way of lessening the dangers which it may carry to the child.

Cow's milk and woman's milk differ materially and grossly in their protein content. The total protein in cow's milk may be nearly three times that contained in woman's milk, but if this were the only difference it might be easily remedied by diluting the cow's milk used in infant feeding. In both milks there are two proteins—casein and albumin, and the proportions of these differ in the two milks. In cow's milk the proportion between casein and albumin is about 5:1, while in woman's milk it is about 1:2. Furthermore, the proteins in the two milks are not exactly of the same composition. The casein of cow's milk is deficient in certain amino acids which are essential to the proper growth of the child. In woman's milk these amino acids are supplied in sufficient amount by the albumin. These differences, while they should be clearly understood, are apparently among the least important of those distinguishing the two foods. In cow's milk the child gets more total protein than it would from its mother's milk, but in the great majority of children the protein is entirely digested and the excess in the cow's milk is essential in order to make amends for its paucity in certain amino acids. In most children artificially fed, evidence that the proteins in cow's milk are not properly digested and completely broken up into amino acids is rare. It will be understood that the child gets an excess of certain amino acids and that this is essential in order that it may obtain a sufficiency of those least abundant in the proteins of cow's milk. There is no evidence that the excess of amino acids taken in when cow's milk is used is a source of danger to the child. So far as the proteins are concerned, the objection to cow's milk is largely due to the formation of large coagula in the stomach. This may be prevented, in part at least, by boiling the milk or by diluting it with barley water or other gruels.

The percentage of carbohydrate in woman's milk and in cow's milk is markedly different, that in the former running about 7.5 and in the latter about 4.7. In both kinds of milk the carbohydrate is, so far as science has as yet determined, the same in kind, being milk sugar or lactose. In both foods the lactose is in complete solution, but when cow's milk is employed the deficiency in this constituent, as compared with woman's milk, must be made good by addition. In selecting a carbohydrate to be added to cow's milk in order to bring its content up to the level existing in woman's milk we have a choice between milk sugar,

cane sugar, and maltose. Theoretically, milk sugar or lactose should be preferred, since it is the normal constituent of both kinds of milk. The cost of milk sugar is somewhat greater than that of cane sugar and the latter is frequently used for this reason. Milk sugar does not ferment with yeast, is not easily broken down in the stomach, and is slightly laxative. It should be added to cow's milk in sufficient quantity to bring the percentage up to six or seven. Lactose is apparently badly borne in many cases, especially when there is an undue tendency to diarrhea. Most children bear cane sugar quite as well as they do milk sugar, but when there is fermentation in the stomach, indicated by vomiting, cane sugar is not desirable. Pure maltose, on account of difficulty in its preparation and its cost, is seldom used in infant feeding. The malt preparations which are employed for this purpose contain dextrins in addition to the maltose. Maltose and its preparations are more easily broken up, both in the stomach and in the intestines, and their administration is not desirable in fermentative diseases of the alimentary canal. It has been found, however, that many children flourish on these preparations and gain in weight more rapidly than when the other sugars are employed. For a long time it was believed that during the early months of life starches are not digested. There is undoubtedly some truth in this, but after the fourth or fifth months infants can easily digest starch in moderation. At any time starch in the form of gruels may be used for the dilution of cow's milk, and these apparently have a good effect inasmuch as they prevent the formation of large coagula of casein in the stomach. On this point, Holt and Howland say:

"Even very young infants are able to digest starch, though their capacity during the early months is limited. After the fourth month it notably increases and after six or seven months most healthy infants can readily digest as much as one ounce of starch daily, and some can do much more than this. This fact makes it possible to use starch in the form of cereal gruels under a variety of conditions when they may be thought desirable. With very young infants their use is mainly as diluents for milk when the coagulation of the casein in the stomach in large masses is an obstacle to digestion. With older infants starches may supply a considerable part of the carbohydrates when there is marked intolerance of all sugars. For the very slow change of the starch into sugar in the intestines is much less likely to cause symptoms than when sugar itself in considerable amount is thrown at once into the intestines. Again, starches are useful to increase the total carbohydrate when all the sugar is being given that the patient can readily tolerate and especially when, on account of intolerance of fats, it is desirable to raise the total carbohydrate to a point considerably higher than is usually given."

The percentage of fat in woman's milk and in cow's milk is practically the same, running normally from 3 to 4, but the fats are not the same in kind. The fat of cow's milk contains from six to eight times the amount of volatile fatty acids found in woman's milk. It is quite

certain that the fat in cow's milk is not as easily digested by the child as that in its normal food. Whether this difference is due to the larger percentage of volatile fatty acids in cow's milk or to some other cause, has not been satisfactorily determined. The digestive disturbances that arise from an excess of fat in artificial feeding are rather serious and are not easily or quickly remedied. For this reason, in beginning artificial feeding the percentage of fat in the prepared food should be reduced to one or two per cent, and pediatricians recommend that at no time during the first year should the percentage of fat in the artificial food be greater than four. It is safer to reach this amount by a gradual increase in the percentage of this constituent.

The inorganic salts present in the two kinds of milk are practically the same in kind, with a slight excess of all in the cow's milk. There is, therefore, no necessity of adding these salts to cow's milk when this food supplants the mother's milk. It has long been customary when slight disturbances occur in artificially fed children to add lime water or bicarbonate of soda to the milk, but this is of questionable value and certainly no such additions should be made except upon the recommendation of a pediatrician.

Besides the chemical differences in the constituents of woman's milk and cow's milk, there are other factors in favor of the natural food, and at least some of these are not susceptible to modification. Fresh milk drawn directly from the mammary gland is more easily and more completely digested than that which is held in some artificial receptacle before it passes into the alimentary canal of the consumer. This is probably true of the milk of all animals and is, partly at least, independent of the conditions under which it is held during the time elapsing between its withdrawal from the gland and its consumption by the young. At least some of the constituents of milk are highly labile and the changes occurring extracorporeally do not improve its fitness as a food. The extent to which these undesirable changes occur in the milk during its transfer from the donor to the recipient are accelerated by high temperature and by bacterial contamination. So far as we know, science has not determined the relative effects of these factors, although it has been assumed that bacterial contamination is more important.

The infant that takes its food exclusively from its mother's breast gets it practically free from any and all contamination, while the child who is fed even upon the best procurable cow's milk takes into its alimentary canal, with every swallow of its food, thousands and ten thousands of bacteria, either living or dead, or in both forms. As we have seen, the New York regulations provide for a Grade A milk which shall not contain more than 60,000 bacteria per c.c., and the very best certified

milk may contain in each c.c. 10,000 bacteria. With all the attention and care that has been given to milk supplies it is safe to say that, although improvements in this food have been great and have led to the saving of many lives, there is today, in our large cities at least, no perfectly safe milk supply. No one can speak with more authority on this point than Park, who has done so much in improving the milk supply of New York, and in 1920 he wrote:

“It is now a well-known fact that the general milk supply of every large city in the world is unfit for use in infant feeding. Two well-defined methods have been applied in New York to effect a change in this respect; first, the production of a special grade of milk, ‘certified’ and allied grades, for infants, and secondly, the general movement to improve the whole supply. Each of these methods has been successful to only a very limited extent. After twenty years, less than one per cent of the city’s milk is of the certified type or equivalent thereto and the expense of this class of milk is almost prohibitive for general use in infant feeding. In fact it is a luxury within reach of comparatively few. What is needed is a safe milk which can be furnished at a price within the means of the masses.”

Fortunately, attempts to render cow’s milk a less dangerous food for infants are continuing with reasonable promise that marked advances and improvements are within the range of possibility. Investigations into the preparation of dried milk and the reassembling of the milk constituents have been undertaken only recently, and one who has used the best of these products scarcely exaggerates when he states that the differences between these and the best market milk are quite as noticeable and marked as those between the raw water of the Potomac and that supplied for drinking purposes to the citizens of Washington. It is true that up to the present time criticism may be made of powdered milk. It may be prepared from skimmed milk or even from adulterated milk, but these objections are remediable. More serious is the claim, substantiated by some experimental work, that the vitamins in the milk are in part destroyed by heating and by long storage.

As we have seen, food is only one of the factors in the causation of the infantile diarrheas and the high death rate that results therefrom. The intelligence of the mother is an important factor, and especial attention to the improvement in this is being given as it has never been before in the teaching of hygiene in our public schools, in the prenatal and child welfare clinics in our cities, and in the dispensaries connected with our milk depot stations. We are not only beginning to realize that the welfare of our nation depends largely upon the attention and care given our children, but this belief has a sufficient grip upon us to lead us to act in accord with it.

Housing conditions must be greatly improved before we can reduce the mortality from the diarrheas of infancy to the lowest possible point.

So long as thousands of dwellers in our large cities live in huts and vile tenements, the infantile death rate from these, as well as from other diseases, will continue to be high. The health department of Chicago has prepared a spot map of that city showing the blocks in which deaths from diarrheal diseases among infants have occurred. Year after year the areas of high death rate have remained unchanged and are located about the stockyards and in other highly congested parts where the ignorant and poor live. In speaking of these areas the health officer says:

"They have remained practically the same for years and are in the districts where population is the greatest; where poverty exists; where the foreign element predominates, and where ignorance is most prevalent."

Into these districts the health department is sending nurses who go from house to house trying to educate mothers how to keep their well babies in health and to send or take their sick babies to infant welfare stations. These efforts are laudable and will do much to reduce the infantile death rate, but so long as people live under the unhygienic conditions now dominating these areas, death will continue to levy a high toll on the innocents. Like tuberculosis, infantile diarrhea is inseparable from the present conditions of life in certain communities. Urban crowding is a phase in our economic life, and we are optimistic enough to believe that it is a passing phase. When our crowded and massive cities and industrial communities are dissipated and their inhabitants take up their residence in garden cities, two very desirable results will follow; both the birth rate and the infantile death rate will fall.

While infant mortality is higher in the poorer districts usually occupied by recent immigrants, there are distinct race stock differences to be noted. Rates are not high among all foreign groups. This is illustrated by Palmer and Blakeslee from a study of the Detroit records for 1919. The rate for the entire city in that year was 97. As shown in the chart, the rate for the children of native-born white mothers was 95, slightly below the average, but there are five race stocks with still lower rates—German, Scandinavian, British, Italian and Russian (mostly Jewish). Children of Russian Jewish mothers had the lowest mortality rate of all the race groups, namely, 64. The highest rate is that of the negro, 151. These racial differences have been found to hold true in other cities as well. On looking into the causes of death among the principal race stocks, we find that the children born of Russian Jewish mothers have low rates in all causes, as classified in the accompanying chart. The Italian is low in all but respiratory disease, where he stands second. In the acute infectious diseases, including venereal and tuberculosis, the negro has a rate nearly double the others. In respiratory

diseases the native white and Russian stand together with low rates, the negro highest, followed by Italian and Austrian. In digestive diseases the Austrian and Polish groups are in a class by themselves with high rates. Diseases of early infancy are equally low with Russian and Italian. The negro has the highest rate, and the distinction between the other three is slight.

Those who can afford to do so should follow the advice given by Rush

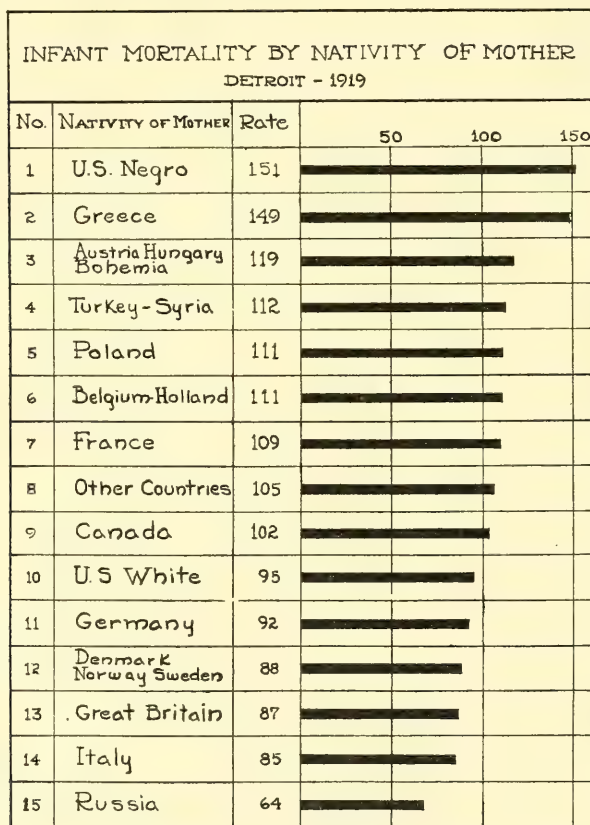


Fig. 12.

more than 100 years ago and take their children during the hot months of summer to the country, but in case the child is being artificially fed attention must be given to the possibility of securing suitable food for the child in the temporary home. It is well known that in many villages and country places there is but little attention given to the securing of a clean milk; in fact, the milk supply of any of our great cities today is likely to be better than that of some villages. Dairy men who produce a milk which cannot be sold in the city have no trouble in disposing of it in the village. In many country places there is no dairy

• INFANT MORTALITY BY CAUSE AMONG RACE STOCKS •

DETROIT-1920

DEATHS UNDER 1 YEAR FROM EACH CAUSE PER 1000 BIRTHS.

NATIVITY OF MOTHER	GENERAL DISEASES. (ACUTE INFECTIOUS, VENEREAL AND TUBERCULOSIS)	RESPIRATORY DISEASES. (PNEUMONIA AND BRONCHITIS)	DIGESTIVE DISEASES .	DISEASES OF EARLY INFANCY INCLUDING MALFORMATION
NATIVE BORN WHITE.	11.2	13.9	21.4	42.1
NEGRO	22.2	44.3	25.6	49.3
RUSSIAN	10.5	11.8	21.0	19.8
ITALIAN	13.0	30.3	19.9	19.0
AUSTRIAN HUNGARIAN BOHEMIAN	12.5	29.4	32.8	40.1
POLISH	11.9	20.0	33.4	40.0

Fig. 13.

inspection, no supervision of the milk sold, and the idea that milk can possibly kill a child has never been entertained by any inhabitant. To escape the heat of the city and go to a place where filthy milk only can be secured is doubtful wisdom. The intelligent mother, however, knows enough to filter the milk through clean cotton, to pasteurize it, to bottle it, to supply herself with the proper nipples, to keep the milk after pasteurization in the refrigerator, to never use one bottle for two feedings, and to make such modifications in the milk as her physician has instructed. It goes without saying that in seeking a summer home for the children local sanitation must not be ignored. Every physician of experience has had opportunity to observe the beneficial effects of country life, under proper conditions, on infants. Even in our larger cities where much of the territory within the city limits is practically rural, infantile diarrhea is rare in the open areas. This is shown very strikingly in the spot map giving the distribution of deaths from infantile diarrhea in Chicago.

Bibliography

- CONDIE, D. F.: *Am. Jour. Med. and Physical Sc.*, New Series, 1825, i, 13.
 CREIGHTON, C.: *A History of Epidemics in Britain*, Cambridge, 1894, University Press.
 GRANT, G. R.: *Am. Jour. Med. Sc.*, New Series, 1853, xxvi.
 HARTSHORNE, H.: *Reynolds System of Medicine*, 1880, iii, 249, Henry C. Lea's Son & Company.
 HIRSCH, A.: *Handbook of Geographical and Historical Pathology*, London, 1886, New Sydenham Society.
 HOLT, L. E., AND HOWLAND, J.: *The Diseases of Infancy and Childhood*, New York, 1916, D. Appleton & Company.
 KING, D.: *Boston Med. and Surg. Jour.*, 1838, xvii, 117.
 LEE, B., HAMILTON, G., ATKINSON, W. B., AND COHEN, J. S.: *Trans. Med. Soc. State of Pennsylvania*, 1872, ix, 191.
 LINDSLY, H.: *Am. Jour. Med. Sc.*, 1839, xxiv, 301.
 MEIGS, C. D.: *Am. Med. Recorder*, 1820, iii, 498.
 PARK, W. H.: *Public Health and Hygiene*, Philadelphia, 1920, Lea & Febiger.
 POTTER, N.: *Baltimore Med. and Surg. Jour. and Review*, 1833, i, 104.
 PRYER, R. W.: *Jour. Lab. and Clin. Med.*, 1916, i, 490.
 ROBERTSON, J. D.: *Report and Handbook of the Department of Health of the City of Chicago for the Years 1911 to 1918 inclusive*.
 RUSH, B.: *Medical Inquiries and Observations*, fourth edition, i, 215, Philadelphia, 1809, M. Carey.
 STEWART, J. A.: *A Practical Treatise on Diseases of Children*, New York, 1841, Wiley & Putnam.
 VAUGHAN, V. C.: *A System of Practical Medicine by American Authors*, iii, 368, Lea Bros. & Company, 1898; *Jour. Am. Med. Assn.*, 1905, xxxiv, 753.
 WEBSTER, J. O.: *Boston Med. and Surg. Jour.*, 1874, lxxxix, 149, 173.

CHAPTER XI

THE TYPHOID FEVERS

Description.—This group includes certain bacteremias which are due to organisms closely related biologically, but differing sufficiently so that immunity to one strain does not give immunity to the others. These fevers are characterized by a step-like increase in temperature day by day until a plateau is reached, after which the temperature decreases step-like until it disappears. The morning temperature is lower than that of the evening and as the fever disappears the morning temperature often falls below the normal. Rose spots usually appear during the second week and are most in evidence over the abdomen. The spleen is usually palpable, but not greatly enlarged. The leukocyte count rarely goes much above the normal and as a rule is below. The average duration of the fever is about 28 days, though it may continue longer and more rarely terminates before that time. In fatal cases characteristic lesions involving Peyer's patches and the agminated glands are found in the small intestines, though death may occur without these lesions. At some time during the course of the disease there is usually more or less marked mental dullness with impairment of the special senses. This condition is common, not only to the typhoid fevers, but to typhus as well; in fact, it gave to all these diseases the original Greek name from the word "typhos," which means a cloud and refers to the mental condition. The case mortality for the fevers of this group, while varying greatly in different epidemics, averages about ten per cent. From an epidemiologic standpoint, these diseases may be considered as one and spoken of in the singular. Differences between members of the group will be brought out later. They are, with certainty, differentiated only by the study of their several causative organisms. They are known as: (1) Eberthian typhoid; (2) paratyphoid A; (3) paratyphoid B. Besides these groups, each of which may be identified, there still remains a number of cases in which the detection of the etiologic agent cannot be made. At present such cases are classified under the general term of "clinical typhoid."

History.—In his writings on epidemics, Hippocrates (fifth century B.C.) describes certain continued fevers with moderate disturbances of the bowels, much wasting and delirium, lasting sometimes 40 days, and recovering rarely by crisis, more frequently irregularly. These can hardly be other than cases of typhoid fever. Galen observed similar cases and described them under the names "hemitritaeus" (used by Hip-

pocrates) and "febris semitertiana." These names were used for centuries. In the seventeenth century Spigelius, writing under the title "De Febre Semitertiana," reports necropsies in which spots and sloughs

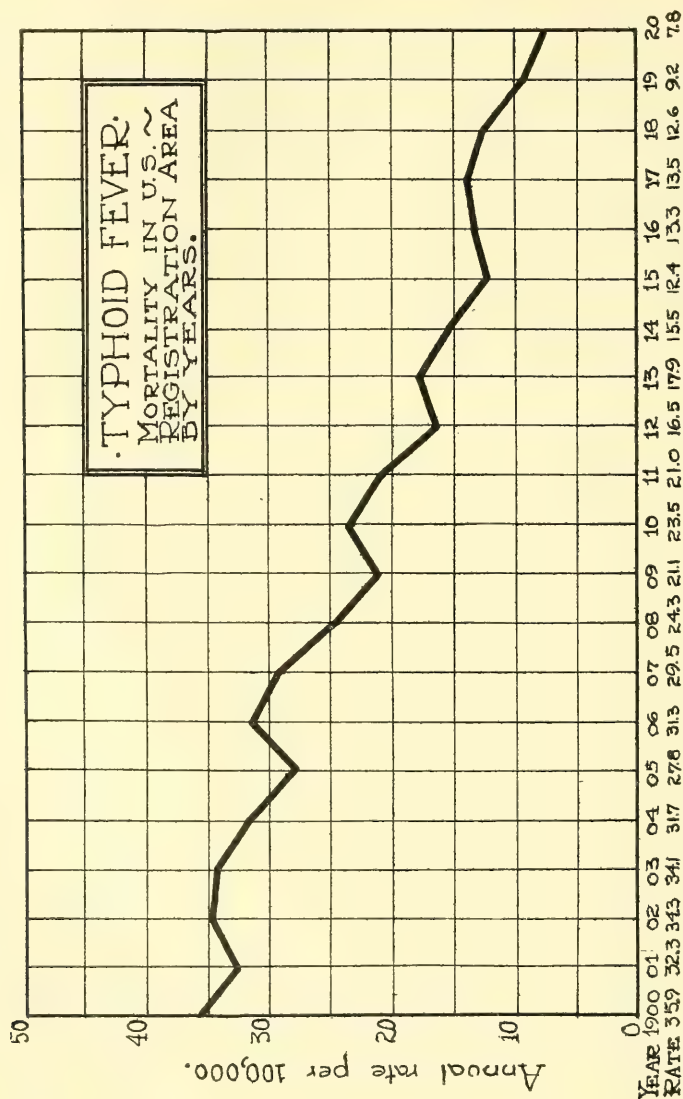


Fig. 14.

were observed in the intestine. Similar lesions were found and reported by other Italian physicians. Near the middle of the same century an English physician, Willis, made necropsies and observed like changes in the intestine. About the same time, the father of English medicine,

Sydenham, described a fever lasting from 14 to 30 days, with a tendency to diarrhea, delirium and epistaxis.

In the eighteenth century many contributions to the knowledge of this disease were made. Morgagni described the intestinal ulcers, perforations, and enlarged mesenteric glands and spleen. Tissot, of Lausanne, gave a good description of the disease, as did Huxham, of England. The latter's picture is sketched in the following words:

"The patient at first grows listless and feels slight chills and sudors with uncertain flushes of heat and a kind of weariness all over. This is always attended by a heaviness and dejection of spirit. A nausea and disrelish of everything soon follow. Though a kind of lucid interval of several hours intervenes, yet the symptoms return with aggravation, especially towards night; the head grows more heavy, the heat is greater, the pulse quicker; a great torpor or obtuse pain affects the head and is commonly succeeded by some degree of delirium. In this condition the patient often continues five or six days, seeming not very sick; about the seventh or eighth day the giddiness, pain or heaviness of the head becomes much greater, often delirium appears with universal tremors and muttering, the tongue grows often very dry, often very thin stools are discharged; now, nature sinks apace; the pulse may be said to tremble and flutter rather than to beat; the sick man becomes quite insensible, and the delirium ends in a profound coma; and that soon in an eternal sleep."

Up to the nineteenth century all the continued fevers with delirium were known under the general name of "typhus." Early in the seventeenth century some of the more observant physicians began to suspect that two quite distinct diseases were included under the diagnosis of typhus and on this point there grew up a discussion which continued for 200 years. That knowledge might be gained to settle this question, necropsies were frequently resorted to and most minute and exact studies of the lesions were made. In a medical way the dispute became, partially at least, an international one. French physicians, led especially by Bretonneau, of Tours, held that in their necropsies they found, quite usually, lesions, inflammatory and ulcerative, in the ileum, while British physicians for the most part failed to find such changes.

The great clinicians of Paris in the early part of the nineteenth century were Trousseau and Louis and these were earnest in presenting their views. At that time many of the brighter young medical men of this country went to Paris to continue their studies. There they heard the lectures and saw the necropsies. Stopping in Great Britain on their visits to and from Paris, they heard lectures and saw necropsies. In France, ulcers were found in the intestines; in England they were not. In this country, some necropsies revealed intestinal lesions while others did not. It soon became evident that there were two distinct diseases, differing not only in the lesions found after death but in onset, progress, and in other respects. The old name, typhus, was retained for

the form without intestinal lesions, and the new term "typhoid" given to that with such lesions. Louis selected the new name, and in giving it he said:

"I have long searched for a word to express the anatomical character of this disease which would not be disagreeable to the ear, and having failed to find such an one, I have adopted the expression 'affection typhoide' as being at least free from inconveniences."

Bretonneau had used the designation "dothinerterie," meaning pustule in the intestine. The word "typhoid" is unfortunate and not so good as

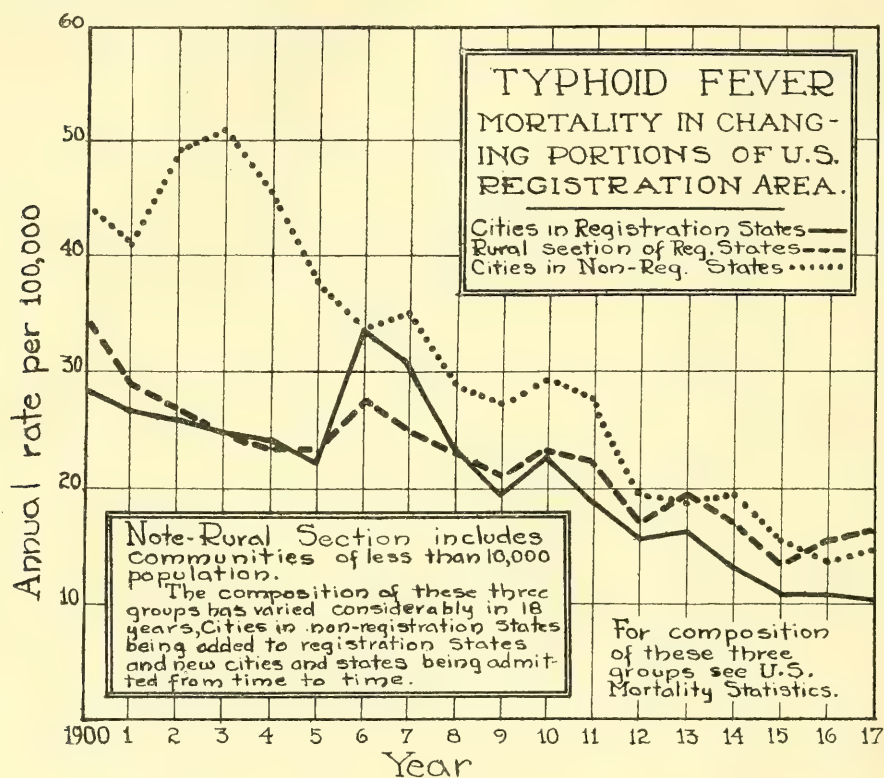


Fig. 15.

the English designation "enteric fever." The Germans know it as "abdominal typhus." Gerhard, of Philadelphia, is generally given credit of finally settling the dispute concerning the duality of the old typhus. Valliex wrote in 1839:

"Gerhard established for the first time the very important fact that there can exist, and there do exist, at the same time in the same country two diseases that may be clearly distinguished and in which one can predict during life the lesions which will be found after death. These diseases are typhoid fever and the true typhus."

Early in our Civil War, medical officers reported fevers which, in their opinion, differed from typhoid fever as seen in the North. The first board appointed (1861) to investigate this matter reported that "the fever prevalent among the soldiers was bilious remittent fever which, not having been controlled in its primary stage, has assumed that adynamic type which is present in enteric fever." A second board was convened (1862) for the purpose of revising the sick report. Major Woodward, the chief of this board, insisted that "the prevailing fevers of the Army on the Potomac were hybrid forms, resulting from the combined influences of malarial poisoning and of the causes of typhoid fever," and he insisted that they should be reported as "typho-malarial fever." This designation became official July 1, 1862, and from that time to June 30, 1866, 57,400 cases with 5,360 deaths, were reported under this name.

While Woodward's designation of the disease was adopted, his understanding of its nature was quite generally ignored. He believed it to be a hybrid resulting from coincident malarial and typhoid infections, while the greater part of the profession understood it to be a severe form of malarial infection. In Woodward's opinion typho-malaria was quite as severe and fatal as typhoid, because it was typhoid in one already infected with malaria or vice versa. He also believed that a trace of scurvy, often unrecognizable until typhoid infection developed, rendered the latter more grave. The majority of physicians and the laity regarded typho-malaria as a severe malaria, but much less grave than typhoid. The new term took a part of the sting out of the diagnosis of typhoid and many a practitioner, in the kindness of his heart, in his desire to spare patients and friends, found the compound word a welcome subterfuge. With the mobilization of troops in the war with Spain (1898) the same fever spread rapidly through the camps, large and small, north and south of the Mason and Dixon line, and was recorded on sick reports under a multitude of names, chiefly malaria, but often typho-malaria and many other designations hitherto and subsequently unused. The board of medical officers appointed to investigate, employing scientific methods of diagnosis, soon showed that malaria was very infrequent and that more than ninety-nine per cent of the cases were typhoid. Among nearly 20,000 cases, 12 of coincident malarial and typhoid infection were found; and even in these the malarial manifestations were suppressed during the course of the typhoid. A man already malarial is not immune to typhoid or vice versa, but even in coincident infection there is no peculiar or characteristic symptom-complex. It follows that "typho-malaria" in any sense is a misnomer and should not be used.

Malaria is not the only infection which may be coincident with typhoid. Cases, though few in number, have been reported in which

typhoid has been coincident with the following: Malta fever, recurrent fever, anthrax, Asiatic cholera, diphtheria, miliary tuberculosis, scarlet fever, and both amoebic and bacterial dysentery. These facts simply show that the above mentioned infections establish no immunity to typhoid nor does this disease protect the individual against other bacterial invasions.

The Causative Organisms.—In 1880, Klebs and subsequently Eberth, published their findings after bacteriologic studies of the bodies of those dead with typhoid fever. Both reported abundant short rods. In addition to these, Klebs found in certain tissues, long, unbranching bacterial forms which he believed to be associated with the disease. He found these organisms in Peyer's patches, in the mesenteric lymph nodes, and in the blood vessels. Eberth stated that the rods which he found, at least some of them, possessed spores and did not readily stain with the ordinary anilin dyes. It is evident that both investigators found the typhoid bacillus and that both were wrong in some particulars. Klebs apparently was wrong in attaching importance to the filamentous growth and Eberth was wrong in attributing the spores to the rods; also in stating that the rods do not readily take the ordinary anilin dyes. To an unprejudiced reviewer of the papers presented by these men it appears plain that Klebs was the original discoverer, but for some reason the name of Eberth has become firmly attached to this bacillus and the fever which it produces is now known as "Eberthian typhoid fever." In 1881, in a second communication, Klebs described a method for the artificial culture of the rods but again his claim was ruled out, and it is generally stated that the credit of cultivating the bacillus typhosus outside of the animal body belongs to Gaffky, who, however, did not report his work until 1884.

There were always some students of this subject, notably Babes and Vaughan, who refused to believe that the Eberthian bacillus is the sole cause of clinical typhoid fever. In 1892, Vaughan, after calling attention to the marked morphologic and cultural differences between the microorganisms found in the spleen after death from typhoid fever, argued that all cases of this disease are not due to a specific organism but to any one of a number of related bacteria. He stated:

"If we cannot agree in this conclusion, we must accept the view of Babes that there are varieties of the Eberth bacillus. It probably makes but little difference whether we conclude that these germs are varieties of one species or that they are related species. I know of no hard and fast lines upon which one can decide, to the satisfaction of every one else, whether two or more germs, differing more or less, should be classified as species or as varieties."

In 1896, Archard and Bensaude reported finding, once in the urine and again in a parotid abscess in cases of typhoid fever, a specific micro-

organism which differs in its sugar reactions from the Eberth bacillus. This is now known as the bacillus of paratyphoid B. In 1897, Gwyn isolated from the circulating blood of a case of clinical typhoid an organism which differed from both the others. This is now known as the bacillus of paratyphoid A. There is an extensive group of bacilli with the typical typhoid at one extreme and the typical colon bacillus at the other and with many intermediate varieties. It is easy to distinguish between the extremes, but it still remains difficult to exactly and satisfactorily locate every member of this group. The Eberth bacillus is motile, sometimes highly, sometimes less freely; it does not coagulate milk; it does not redden litmus milk; it forms blue colonies on plates of gelatin colored with litmus; when grown in whey, colored with litmus it produces only slight cloudiness and at most only slightly reddens the medium; when grown in fermentation tubes in solutions containing lactose, raffinose, or saccharose, it produces neither acid nor gas; when grown in solutions containing glucose, levulose, maltose, galactose, dulcitate, or mannite, it may produce small amounts of acid but it does not produce gas; on Endo medium its colonies are colorless; grown in Drigalski medium its colonies are blue and transparent; it blackens subacetate of lead; it produces no indol; when grown in beef broth its cultures have no significant odor and do not form a pellicle.

Bacillus paratyphosus A, when grown in solutions of lactose, raffinose, or saccharose, produces neither acid nor gas; in solutions containing glucose, levulose, maltose, galactose, dulcitate, or mannite, it produces both acid and gas; on Endo medium its colonies are colorless; on Drigalski medium its colonies are blue and transparent; it does not blacken subacetate of lead; it produces no indol; when grown in beef broth its cultures have a slight odor.

Bacillus paratyphosus B, when grown in solutions containing lactose, raffinose, or saccharose, produces neither acid nor gas; when grown in solutions containing glucose, levulose, maltose, galactose, dulcitate, or mannite, it produces both acid and gas; on Endo medium its colonies are colorless; on Drigalski medium its colonies are blue and transparent; it blackens subacetate of lead; it produces no indol; when grown in beef broth its cultures have a disagreeable fecal color and it forms pellicles.

Cultures of the colon bacillus have a distinct fecal odor; the organism is slightly motile, sometimes nonmotile; it coagulates litmus milk, produces strong acid in a few hours; when grown in solutions containing lactose, raffinose, or saccharose, it produces both acid and gas; the same is true when grown in solutions containing the other sugars; on Endo medium its colonies are red; on Drigalski medium its colonies are

red and opaque; most strains do not blacken subacetate of lead; it produces indol.

It will be seen from the above-mentioned facts that it requires somewhat of an expert to distinguish at all times between these organisms. Clinically, the distinction is usually made by obtaining pure cultures in cases of typhoid fever from the blood, the urine, or the feces, and testing the agglutinating properties of the culture thus obtained with specific sera. The blood of a case of typhoid fever due to any one of the three species or varieties does not agglutinate, at least in high dilution, the other organisms. This is the method employed in distinguishing the three varieties of typhoid fever. Whether other varieties will be detected or not remains for the future to determine. As has been stated, there are cases of clinical typhoid fever in which no specific organism has as yet been detected in the blood, urine, or feces.

Transmission.—When typhoid fever was first distinguished from typhus fever the former was supposed not to be transmissible. This conclusion, however, was reached simply by comparison with typhus fever. Some of the keener observers in the early part of the nineteenth century, especially Leuret (1828), Bretonneau (1829), Gendron (1834), and Piedvache (1850), came to the conclusion that typhoid fever is to a limited extent contagious or transmissible. The first to show how this disease is transmitted was an English physician by the name of Budd, who began his publications on this subject in 1856. By close epidemiologic study he showed that water or milk contaminated with the feces of one sick with typhoid fever may transmit the disease to others. He laid special emphasis upon this fact and stated: "This method of reproduction is not only a characteristic but the master fact in the history of typhoid fever." It is interesting to note that he went so far as to point out that the stools of those convalescing from typhoid fever may serve in the transmission of this disease. Indeed, he stated the transmission of this disease is always caused by the transfer of the dejections from the infected, either directly or indirectly, to the mouth of the one to receive the infection. He said that a sewer is only a prolongation of the alimentary tract of the infected person.

Murchison, who wrote abundantly and learnedly upon this subject (1850-1884), also believed that typhoid fever may be transmitted by polluted water or milk. However, he believed that this disease may originate *de novo*. In other words, he taught that the feces from healthy persons, as well as other kinds of filth, undergoes outside the body a process of fermentation during which the virus of this disease is produced. This was known as the "pythogenic theory" and it did much to retard the scientific advancement of knowledge concerning the true etiology of the disease.

About the middle of the nineteenth century, Munich was the very hot bed of this disease. At that time there came to this city a young, intelligent epidemiologist, one of the first of his kind, by the name of Pettenkoffer. The city was honey-combed with privy vaults and shallow wells. The contents of the former leached into the latter from which the people drank. Pettenkoffer taught that the filth in the soil undergoes a ripening process in which the virus of typhoid fever is elaborated. This doctrine came to be known as the "ground-water theory." Pettenkoffer advised that the privies be closed, that sewers be introduced, and that a pure water-supply be brought direct from a mountain lake many miles distant. His advice was followed and resulted in the eradication of this disease to such an extent that of all the capitals of Europe Munich had the lowest death rate from typhoid fever. Vienna followed the example and secured a similar result. Thus, it is seen that even an erroneous theory may lead to great improvement in the well-being of the people. From an annual death rate per 100,000 of 203 from 1857-1867, the decrease in Munich was continuous, and from 1901-1910 it averaged 2.5. Even the small figure shown in the last given decennium was due to those who acquired the infection in other localities. This is probably the most striking and the best illustration of what may be accomplished in the eradication of this disease by purely sanitary measures.

Water-Borne Typhoid.—The results obtained in Munich and Vienna were sufficiently striking to arouse the attention of the civilized world and cities began to seek uncontaminated water-supplies, to forbid the use of privies within their limits, and to improve their sewerage. Quite naturally, European cities led in this work. However, American cities have followed and today, apart from war conditions, there is no large city in the civilized world which does not more or less effectively guard its water-supply. It is true that the death rate in Petrograd from water contamination continued to be excessive up to the time of the war and probably has not decreased under Soviet rule. In 1910 the death rate from this disease in that city was 33.7 per 100,000.

Man has demonstrated that there is no body of fresh water in the world so large and so pure that he may not dangerously contaminate it, certainly in some localities. For many years Chicago took its water supply from Lake Michigan, and at the time of the World's Fair at that place (1893) there were more than 30 public sewers and innumerable private ones emptying their contents into the same water. It is needless to say that at that time the death rate from typhoid fever in Chicago was high. Indeed, it was so alarming as to threaten the success of the exposition and a private water line was laid from Waukesha, Wisconsin, to the exposition grounds.

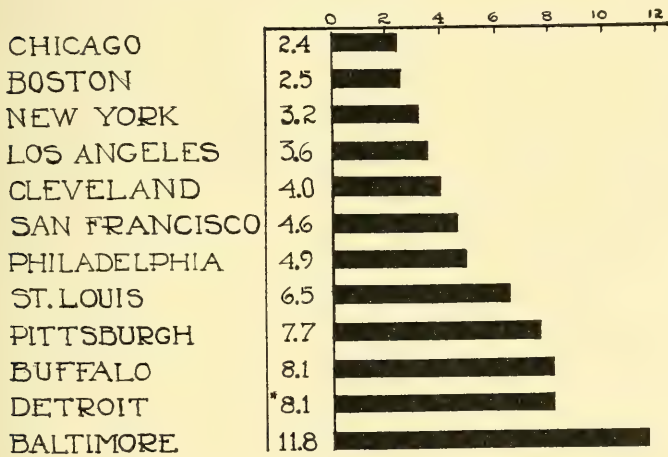
There is probably nowhere on the surface of the earth a larger or purer water-supply than that contained in Lake Superior. Yet, at both ends of this great lake, to say nothing of places along its border, the water has been so contaminated as to cause serious outbreaks of typhoid fever. In the early nineties of the last century Duluth put its water-crib in the lake and emptied its sewage into the same body of water, not far distant. In January, 1891 there was a severe epidemic of typhoid fever in that city, with more than 1,500 cases developing within two or three weeks. During the epidemic Vaughan examined four samples of this water, one of which was taken from a tap in a doctor's office, the occupant of which had gone home some days before with typhoid fever, and so far as known the tap had not been used since he left the office. In this sample a typhoid-like bacillus was found. No suspicious organism could be detected in the other samples. About the same time the city of Sault Ste. Marie was taking its water-supply above the rapids, having the whole of Lake Superior as its reservoir. In the fall of 1890, owing to a break in the lock, more than 200 boats were detained for two days above the lock and in the immediate vicinity of the intake. Nearly 400 cases of typhoid fever developed within a few days in that city. The same epidemiologist found a toxicogenic bacillus in the water at the height of the epidemic. A month later the water from this source contained less than 100 bacteria in each c.c. and among these there was no suspicious organism. Milwaukee, Traverse City, Port Huron, St. Clair and Detroit have had similar experiences. Water-borne typhoid fever usually manifests itself, especially when the contamination is great and sudden, by an explosive outbreak, many cases of the disease appearing almost simultaneously.

The introduction of filtration and sterilization for water-supplies has had a marked effect on the incidence of the disease in many cities. Mills, Sedgwick, Whipple, Kober, Johnson and many others have written voluminously on the subject. The Massachusetts State Board of Health Report for 1892 contains accounts of water-borne epidemics at Lowell and Lawrence. Both cities drank water from the sewage-polluted Merrimac River. Great epidemics broke out in both cities in 1890. The Lowell epidemic was traced to an unusual infection on Stony Brook, a small tributary of the Merrimac. The Lawrence epidemic followed shortly after, being due to the Stony Brook infection and also to the typhoid polluted sewage from Lowell, which was discharged into the river only nine miles above the Lawrence intake. Nearly fifteen hundred cases of typhoid occurred at this time in these two cities. Lowell changed to driven wells as a source of water, with a consequent reduction from a general average typhoid death rate of 80 to one of 20. Lawrence, on the other hand, installed a slow sand filtration plant. From a rate of

120 prior to 1892, typhoid fell in a few years' time to a level of 20. Among cities with similar experiences may be mentioned Albany, Binghamton, Watertown, all in New York, Paterson, N. J., and Trenton, N. J. Newark cut its typhoid mortality to one-third by shifting its water-supply from the polluted Passaic River to the unpolluted Pequannock. Jersey City likewise reduced its typhoid by abandoning the polluted Passaic in favor of less polluted streams. Hazen estimates that in 1900 about 6.3 per cent of the urban population of the United States

TYPHOID FEVER MORTALITY IN THE 12 U.S. CITIES WITH OVER 500,000 POPULATION.

AVERAGE RATES FOR 5 YEAR PERIOD 1916-1920



*Detroit rate based on corrected population following 1920 census. Rate using former census estimate of population is 10.6.

Data from Journal A.M.A.
March 26, 1921.

Fig. 16.

was receiving filtered water. By 1904 this had increased to 9.7 per cent and in 1913 to 20 per cent. Fuller places the figure at 33 per cent in 1921.

A record of typhoid prevalence in United States cities is furnished by the *Journal of the American Medical Association*. It has been customary each year since 1913 to present a summary of typhoid death rates during the preceding year. There are available from this source average death rates for three five-year periods, namely, 1906 to 1910, 1911 to 1915 and 1916 to 1920. This material, which we reproduce in tabular form, gives us an illuminating picture of the universal decline

in typhoid throughout the larger cities in this country. The cities are grouped by size on the basis of the 1920 census. We have omitted several cities for which 15 year records are incomplete.

TABLE IX

DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF MORE THAN 500,000 POPULATION

ANNUAL RATE PER 100,000					
Group I.					
1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. New York	13.5	1. New York	8.0	1. Chicago	2.4
2. St. Louis	14.7	2. Boston	8.0	2. Boston	2.5
3. Cleveland	15.7	3. Chicago	8.2	3. New York	3.2
4. Chicago	15.8	4. Cleveland	10.0	4. Los Angeles	3.6
5. Boston	16.0	5. Los Angeles	10.7	5. Cleveland	4.0
6. Los Angeles	19.0	6. Philadelphia	11.2	6. San Francisco	4.6
7. Detroit	21.1	7. St. Louis	12.1	7. Philadelphia	4.9
8. Buffalo	22.8	8. San Francisco	13.6	8. St. Louis	6.5
9. San Francisco	27.3	9. Buffalo	15.4	9. Pittsburgh	7.7
10. Baltimore	35.1	10. Pittsburgh	15.9	10. Buffalo	8.1
11. Philadelphia	41.7	11. Detroit	18.1*	11. Detroit	10.6*
12. Pittsburgh	65.0	12. Baltimore	23.7	12. Baltimore	11.8
Average	25.6		12.9		5.8

Data from Journal of American Medical Association, March 26, 1921.

*Based on corrected populations, Detroit's average from 1911-15 was 14.8 and from 1916-20, 8.1. Journal A. M. A. did not correct previous average rates following 1920 census.

TABLE X

DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF FROM 300,000 TO 500,000 POPULATION

ANNUAL RATE PER 100,000					
Group II.					
1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. Newark	14.6	1. Seattle	5.7	1. Seattle	2.9
2. Seattle	25.2	2. Newark	6.8	2. Newark	3.3
3. Milwaukee	27.0	3. Cincinnati	7.8	3. Cincinnati	3.4
4. Cincinnati	30.1	4. Minneapolis	10.6	4. Minneapolis	5.0
5. Indianapolis	30.4	5. Milwaukee	13.6	5. Milwaukee	6.5
6. Minneapolis	32.1	6. Kansas City	16.2	6. Washington	9.5
7. New Orleans	35.6	7. Washington	17.2	7. Indianapolis	10.3
8. Kansas City	35.6	8. Indianapolis	20.5	8. Kansas City	10.6
9. Washington	36.7	9. New Orleans	20.9	9. New Orleans	17.5
Average	29.7		13.2		7.7

Data from Journal of American Medical Association, March 26, 1921.

In the cities of Group I, having over 500,000 population, New York was lowest in the first period, 1906 to 1910, with a rate of 13.5. In the next five year period New York's rate fell to 8.0, and in the third period, from 1916 to 1920, there was a further drop to the unusually low figure of 3.2. At the lower end of the table, or in 12th place in 1906-10, stood

TABLE XI

DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF FROM 200,000 TO 300,000
POPULATION

ANNUAL RATE PER 100,000

Group III.

1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. Jersey City	12.6	1. Jersey City	7.2	1. Rochester	2.9
2. Rochester	12.8	2. Oakland	8.7	2. St. Paul	3.1
3. Providence	14.3	3. St. Paul	9.2	3. Oakland	3.8
4. St. Paul	18.3	4. Rochester	9.6	4. Providence	4.4
5. Oakland	21.5	5. Providence	10.2	5. Portland, Ore.	4.5
6. Portland, Ore.	23.2	6. Portland, Ore.	10.8	6. Jersey City	4.5
7. Toledo	37.5	7. Denver	12.0	7. Denver	5.8
8. Denver	37.5	8. Columbus	15.8	8. Columbus	7.1
9. Columbus	40.0	9. Louisville	19.7	9. Louisville	9.7
10. Louisville	52.7	10. Toledo	31.4	10. Toledo	10.6
11. Atlanta	58.4	11. Atlanta	31.4	11. Atlanta	14.2
Average	29.9		15.1		6.4

Data from Journal of American Medical Association, March 26, 1921.

TABLE XII

DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF FROM 150,000 TO 200,000
POPULATION

ANNUAL RATE PER 100,000

Group IV.

1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. Worcester, Mass.	11.8	1. Worcester, Mass.	5.0	1. Worcester, Mass.	3.5
2. Syracuse	15.6	2. Syracuse	12.3	2. Omaha	5.7
3. Dayton	22.5	3. Dayton	14.8	3. New Haven	6.8
4. New Haven	30.8	4. Omaha	14.9	4. Syracuse	7.7
5. Richmond	34.0	5. Richmond	15.7	5. Dayton	9.3
6. Memphis	35.3	6. New Haven	18.2	6. Richmond	9.7
7. Omaha	40.7	7. Memphis	42.5	7. Memphis	27.7
Average	27.2		17.6		10.1

Data from Journal of American Medical Association, March 26, 1921.

TABLE XIII

DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF FROM 125,000 TO 150,000
POPULATION

ANNUAL RATE PER 100,000

Group V.

1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. Bridgeport, Conn.	10.3	1. Bridgeport	5.0	1. Scranton	3.8
2. Hartford, Conn.	19.0	2. Paterson	9.1	2. Bridgeport	4.8
3. Paterson, N. J.	19.3	3. Scranton	9.3	3. Hartford	6.0
4. Grand Rapids, Mich.	29.7	4. Hartford	15.9	4. Paterson	6.7
5. Scranton, Pa.	31.5	5. Grand Rapids	25.5	5. Grand Rapids	9.1
Average	22.0		13.0		6.1

Data from Journal of American Medical Association, March 26, 1921.

TABLE XIV
DEATH RATES FROM TYPHOID FEVER IN U. S. CITIES OF FROM 100,000 TO 125,000
POPULATION

ANNUAL RATE PER 100,000					
Group VI.					
1906-1910		1911-1915		1916-1920	
ORDER CITY	RATE	ORDER CITY	RATE	ORDER CITY	RATE
1. Cambridge, Mass.	9.8	1. Cambridge	4.0	1. Yonkers	2.2
2. Yonkers, N. Y.	10.2	2. Yonkers	8.5	2. Cambridge	2.5
3. Fall River, Mass.	13.5	3. Lowell	10.2	3. Tacoma	2.9
4. Lowell, Mass.	13.9	4. Tacoma	10.4	4. Spokane	4.9
5. New Bedford, Mass.	16.1	5. Fall River	13.4	5. Lowell	5.2
6. Albany, N. Y.	17.4	6. New Bedford	15.0	6. New Bedford	6.0
7. Tacoma, Wash.	19.0	7. Spokane	17.1	7. Albany	8.0
8. Reading, Pa.	42.0	8. Albany	18.6	8. Fall River	8.5
9. Spokane, Wash.	50.3	9. Reading	31.9	9. Reading	10.0
10. Nashville, Tenn.	61.2	10. Nashville	40.2	10. Nashville	20.1
Average	25.3		16.9		7.1

Data from Journal of American Medical Association, March 26, 1921.

Pittsburgh with a rate of 65.0. In the succeeding five years this rate fell to 15.9, placing Pittsburgh in 10th place, and in the third period the rate was 7.7, or 9th place among the largest cities. It is significant that Baltimore, the 12th city in the last period, with a rate of 11.8, has a lower figure than New York, which stood in first place in 1906-10 with a rate of 13.5. The most noticeable improvement in relative positions was attained by Philadelphia, which rose from 11th place in 1906-10 to 7th place in 1916-20.

In the cities of Group II, with populations from 300,000 to 500,000, Newark and Seattle have consistently held either first or second place in the three periods. Washington stood last in 1906-10 with a rate of 36.7 but moved up to 6th place in 1916-20 with a rate of 9.5. New Orleans had the poorest rate in 1916-20, the figure being 17.5. The cities of the third group, population 200,000 to 300,000, had rates ranging from 12.6 to 58.4 in the first period and from 2.9 to 14.2 in the last. Rochester, N. Y., has consistently maintained its position near the top. There are seven cities in Group IV with rates in 1916-20 ranging from 3.5 to 27.7, the latter figure being that of Memphis, Tenn. Worcester has led these cities in all three periods. Omaha rose from seventh, or last place, in the first, to second place in the third period. In the last two groups of cities, Scranton, Pa., shows an improvement from a rate of 31.5 in 1906-10 to 3.8 in 1916-20. Spokane, Wash., likewise evidences a remarkable drop in typhoid, the rate in 1906-10 being 50.3 and in the most recent period 4.9, which is less than one-tenth the former rate. Considering the entire list of cities, Cambridge, Mass., had the lowest rate from 1906 to 1910,

namely, 9.8, also the lowest rate in 1911-1915, or 4.0; Yonkers, N. Y., the lowest in 1916-20, or 2.2. The poorest rate in the first period was that of Pittsburgh (65.0); in the second period Memphis (42.5); in the third period Memphis 27.7.

In this last period it is the largest cities of the country which have collectively the lowest typhoid death rate, namely, 5.8. Group V stands second with 6.1, Group III 6.4, Group VI 7.1, Group II 7.7 and last, Group IV 10.1. Of all the cities from which records are available, the ten with the lowest typhoid fever death rates for the five years ending in 1920 are:

Yonkers	2.2
Chicago	2.4
Boston	2.5
Cambridge	2.5
Seattle	2.9
Rochester	2.9
Tacoma	2.9
St. Paul	3.1
New York	3.2
Newark	3.3

Stating the typhoid situation in general terms, we may say that for every 4 deaths in the period of 1906-10, there were 2 in 1911-15 and only 1 in 1916-20.

The cause of this decline has been largely due to the substitution of safe water for polluted water. Many cities have, during this period, installed filtration plants or chlorin equipment for the disinfection of water-supplies, and the history of individual cities is striking testimony of the immediate improvement in the typhoid situation as the result of the use of safe water. The chart for Trenton, N. J., is but one example, and the same experience has been duplicated by Pittsburgh, Philadelphia, Albany and numerous other cities. Credit must also be given, of course, to the elimination of open privies accessible to flies and domestic animals, to the wide extension of the uses of pasteurized milk, to the improved methods for detecting typhoid carriers and to the elimination of such carriers in food handling occupations.

Improvement in water-supplies has been credited with a reduction in deaths from other causes as well as typhoid fever. In 1910 Sedgwick and MacNutt gave publicity to the Mills-Reinke Phenomenon and to Hazen's Theorem. The first was the outcome of the independent observations in 1893-94 by Hiram F. Mills, C. E., of Lawrence, Massachusetts, and Dr. J. J. Reinke of Hamburg, Germany, that the purification of public water-supplies effected a decline in the total death rate in a way not wholly accounted for by the reduction in typhoid. In 1904 Allen

Hazen concluded from a study of the work of Mills and Reineke and from later observations of his own that "where one death from typhoid fever has been avoided by the use of better water, a certain number of deaths, probably two or three, from other causes have been avoided." Various reasons have been advanced to explain this result. While it is not difficult to understand that better water might lessen the general mortality among babies and young children, especially from diarrheal diseases due to water or to milk diluted with water, it is not so easy to believe that pneumonia and tuberculosis and other diseases associated

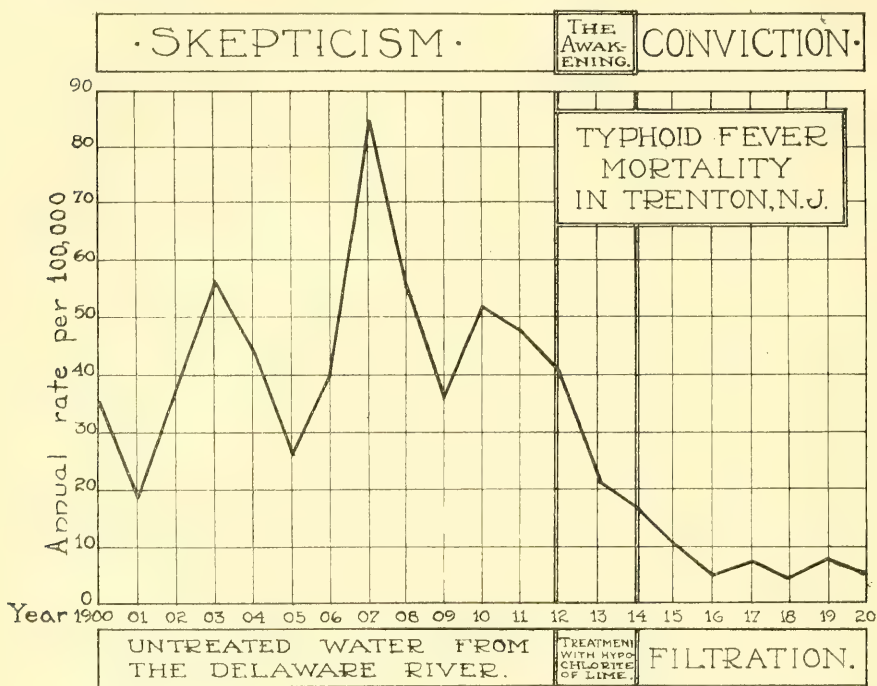
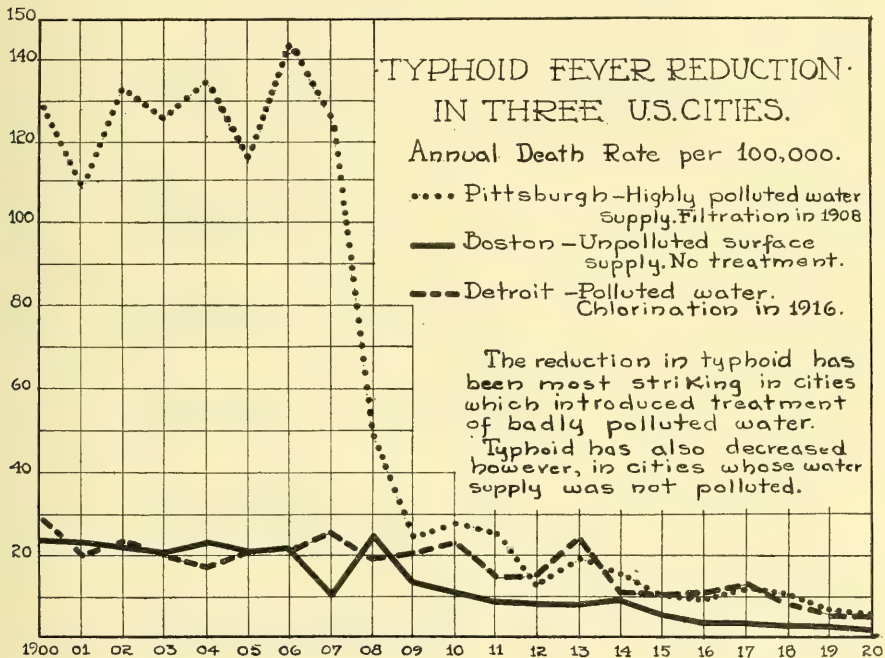


Fig. 17.

with adult life would be markedly affected. Guided by the experience of recent years it is our opinion that the Mills-Reineke Phenomenon, in so far as it is related to respiratory diseases, was based on faulty premises. The original suggestion came from the experiences of Hamburg, Lowell and Lawrence in the decade 1890-1900. The improvement in the general death rate was represented by the years subsequent to 1893. This was contrasted with the years prior to this date. It will be recalled that the great influenza pandemic began in December, 1889, and continued with recurrent waves until 1894. The reduction in the general death rate after 1893 was coincident with the introduction of better water in the three cities mentioned. The reaction from the influ-

enza epidemic was marked by a low mortality, just as has been observed in 1920 and 1921, following the pandemic of 1918. Thus what appeared to result in Lawrence, Lowell and Hamburg from better water has not been borne out to the same extent in some cities and not at all in others. Deaths from acute respiratory diseases in Albany fell off precipitously after 1891, 8 years before filtration. Following filtration in 1899 they dropped slightly. No such decline in the general death rate followed in Binghamton, where filtration began in 1902, or in Watertown, where filtration went into effect in 1904. Though Hazen's Theorem has not



Note—Pittsburgh figures are combined rates for Pittsburgh and Allegheny which consolidated in 1908.

Fig. 18.

been substantiated by subsequent experience, there is some ground for expecting a decline in mortality in diseases other than typhoid. Recently Dublin has shown from a study of death rates among holders of insurance policies that for the first two or three years after recovery from typhoid fever the death rate among these recovered people is more than twice the normal rate. In other words, those who recover from typhoid fever are for two or three years thereafter more liable to other infections than are people who have not had the disease.

We might say that the reduction in urban typhoid has even exceeded our expectations. Chicago's rate for 1920 was 1.1. Admitting that Chi-

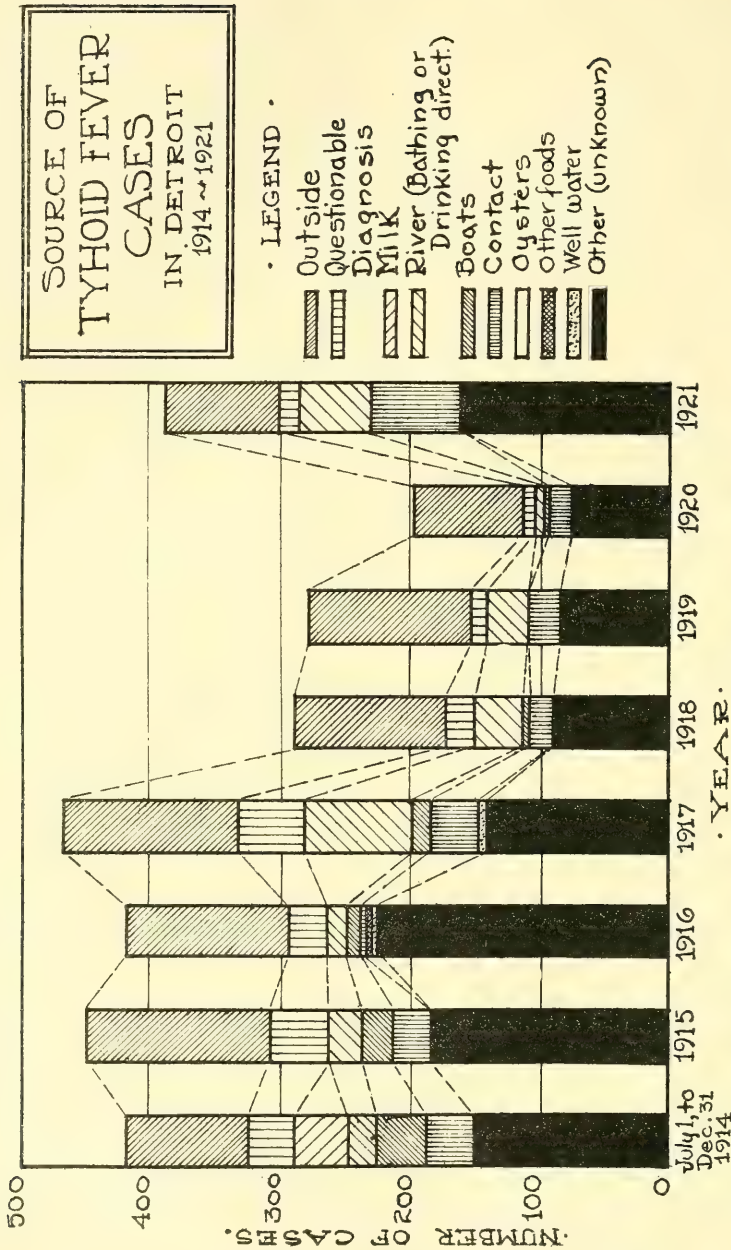


Fig. 19.

icago's milk and water-supply are so pure that no case of typhoid fever results therefrom, it is difficult to believe that residents of Chicago would not bring more typhoid fever into the city acquired in other places than is indicated by these figures. Vaccination for typhoid fever

is not generally practiced, nor so far as we know, is it practiced at all in the city of Chicago. If so good a result can be obtained without vaccination, there remains no great argument for the recommendation or enforcement of this procedure in civilized communities. As the *Journal of the American Medical Association* points out, the records bearing on this point from New York are probably the most reliable. In 1918, for example, 135 cases were attributed to out-of-town infection, 23 to milk contamination and 83 to contact. It should be remarked that these figures cover only the third quarter of the year.

Since 1914 it has been customary in Detroit to visit every case of typhoid reported. So far as possible, the source of the disease has been determined. Of those cases where definite information could be obtained, the most common cause of Detroit cases was infection contracted outside the city. This amounts to about 30 per cent. Infection from drinking and bathing in polluted river water makes up about 10 per cent. Contact infection accounts for 8 per cent. Some causes have been notably reduced since 1914. Thus, milk accounted for 44 cases in 1914 but none since, a single exception occurring in 1921. Infection contracted from drinking water on the Great Lakes boats accounted for 4.7 per cent of all cases prior to 1918 and only 0.7 per cent since that time. Improvement in diagnosis is to be noted. Prior to 1918, 9.3 per cent of cases were questionably diagnosed. In the last four years only 5.2 per cent have been placed in this category.

TABLE XVI
SOURCES OF TYPHOID FEVER CASES IN DETROIT

SOURCE	JULY 1, 1914— DEC. 31, 1917		JAN. 1, 1918— DEC. 31, 1921.	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
Outside	505	28.4	416	35.8
Ques. Diag.	165	9.3	60	5.2
Milk	44	2.5	1	0.1
River	149	8.4	132	11.4
Boats	83	4.7	9	0.7
Contact	111	6.2	129	11.1
Other (Unknown)	702	39.5	412	35.5
Oysters	3	0.2	0	0.0
Other Food	3	0.2	0	0.0
Well Water	11	0.6	3	0.3
	1776		1162	

Procedures for the protection of municipal water-supplies must depend upon and be determined by local conditions. The most natural thing to do is to go to uncontaminated sources, such as mountain lakes and barren plains situated in regions where contamination is practically impossible. This was the method followed by Munich and Vienna.

Most of the larger Italian cities have done the same thing. In some instances an abundance of potable water is found by sinking wells in barren and sparsely inhabited areas; however, it is exceedingly rare to find enough water to supply a large city in such districts. There are large parts of the earth covered by sand and gravel deposits which form filter beds that surpass anything that man can build, but in most of these localities the soil has already been contaminated by man. New York City has always had a relatively low death rate from typhoid fever. For many years it secured safe water by preventing contamination of the Croton watershed. This the city was able to do as a result of legislative enactment, because the whole of the watershed lay without the city's jurisdiction. This supply having proved inadequate, New York at great cost has gone to the Catskill Mountains for its supply. Most cities are so situated that they must obtain their supply from sources which are liable to pollution. This has necessarily led to the development of methods of water purification. Filtration and proper chlorination have been so well developed that even a polluted stream may furnish safe drinking water. It is not within the province of an epidemiologist to go into detail concerning the methods of water purification. This belongs to the sanitary engineer, and it must be admitted that when given the opportunity he has done his work with commendable skill and success.

The introduction of pure water-supplies will not wholly eliminate typhoid fever from our cities. It has proved to be true that there are always those who will not use the public water-supply, however excellent it may be, but will continue to drink from polluted wells and other contaminated sources. Then, there is the greedy manufacturer, who, to save the small expense incurred in using the city supply, will run a private line into some contaminated source and thus introduce the disease among his employees. Instances of this have frequently come to light. Many dwellers in cities spend days or weeks during the summer in the country, where they are ready apparently to accept without question the water-supply of any locality. It follows that the death rates from this disease even in cities supplied with the purest waters increase with the return of those who have been recuperating their health at the seashore, in the mountains, in some village, or on some farm. From infections acquired outside the city, a certain number of secondary cases due to contact invariably occur.

The small town or growing city which is in the transition stage between private well water and a public piped supply has a difficult problem to solve. There are many citizens loath to abandon the grand, cold, sparkling well waters raised by the old oaken bucket and the chain pump. Usually these waters are badly polluted by seepage from cess-

pools and privies. Under these circumstances the introduction of filtration in a city in which only part of the inhabitants are reached by the public supply may not show an immediate reduction in typhoid. Youngstown, Ohio, is an example. Hansen, of the Ohio State Board of Health, found that out of 153 cases occurring in the early part of 1906, 93 resided in houses where there were no sewers and no public supply, and 109 claimed to have used well water only. The outbreak was attributed to polluted wells and direct contact, including transmission by flies.

Bowen, epidemiologist of the New Jersey State Board of Health, reports an epidemic of 71 cases traced to a polluted well in Roebling, N. J. In the course of a previous investigation, recommendation had been made that this well be discontinued because of its dangerous sur-

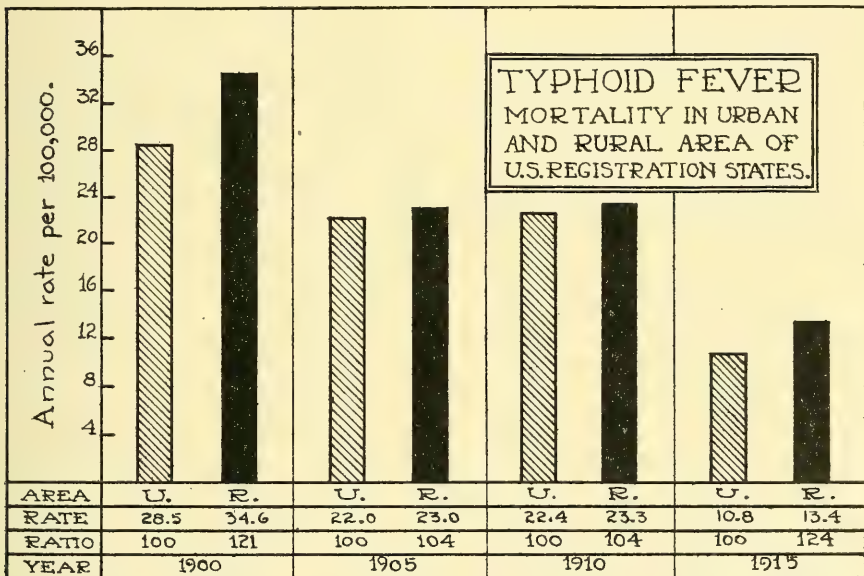


Fig. 20.

roundings. This advice was ignored. Later, or in October, 1912, typhoid appeared with a sudden flareup. The investigation developed that the cases were largely confined to men working in one of the shops. Of seventy-one cases that occurred, 63 were men actively engaged in the Roebling Works. Eight cases not among male workers included 6 children and two women. The male cases were confined to a few buildings which were not reached by the town water-supply. Employees either carried water from the taps in other buildings or from a spring on the hillside some distance away, or from a well conveniently located on adjoining property. Although the employees in this group of buildings constituted less than one-third of the total force; yet they fur-

nished all of the typhoid cases. The well in question was a dug well about fifteen feet deep. It was located beneath the floor of a shed attached to the rear of one of four two-family frame dwellings, known locally as "Knickerbocker Row." Open seams in the board floor covering the well permitted polluting material from the unclean floor to fall directly into the well. The surrounding ground was grossly polluted. A box drain for waste liquids bordered the well and connected with a drain running to the river. Information was obtained of two children who had been ill in the house adjoining the well during October. One of the cases showed a positive Widal. Facts regarding the other case were incomplete. The people were foreigners unfamiliar with English, and it was very difficult to secure reliable information from them. A sample of well water collected on November 8 yielded the typhoid bacillus. The well was closed to the public on October 28 and no cases occurred two weeks after this date.

No one has been more regardless of the water supplied his family than the isolated farmer. He digs his well without reference to geological formations and he seems possessed with the idea that he must get his privy vault and his cesspool as close to the well as possible. For this and other reasons strictly rural communities are often badly infected with this disease.

Numerous and serious outbreaks of diarrhea and typhoid fever have occurred in the crews and among the passengers on our river and lake boats. In one short season several hundred who enjoyed a vacation on one of the most palatial steamers plying the Great Lakes were stricken with this disease. Similar facts were observed on one or more of the Mississippi boats. These occurrences became so frequent and so serious that the matter demanded and received federal investigation. At that time the drinking water-supply of most steamers was taken through pipes perforating the bottom of the vessel. The drinking water tanks were filled whenever and wherever the demand appeared. It sometimes happened that the pumps were set going in most highly polluted harbors. However, the more intelligent captains forbade this. With the immense tonnage of the Great Lakes, and with boats plying practically the same lanes, hundreds in a procession, with innumerable cities pouring their sewage into the lakes, with storms tossing and mixing waters, it is safe to say that even in these great bodies of water it is dangerous to take on a drinking supply at any point without purification. Federal regulations demand the sterilization of water used for drinking purposes on the boats of the Great Lakes and the large rivers.

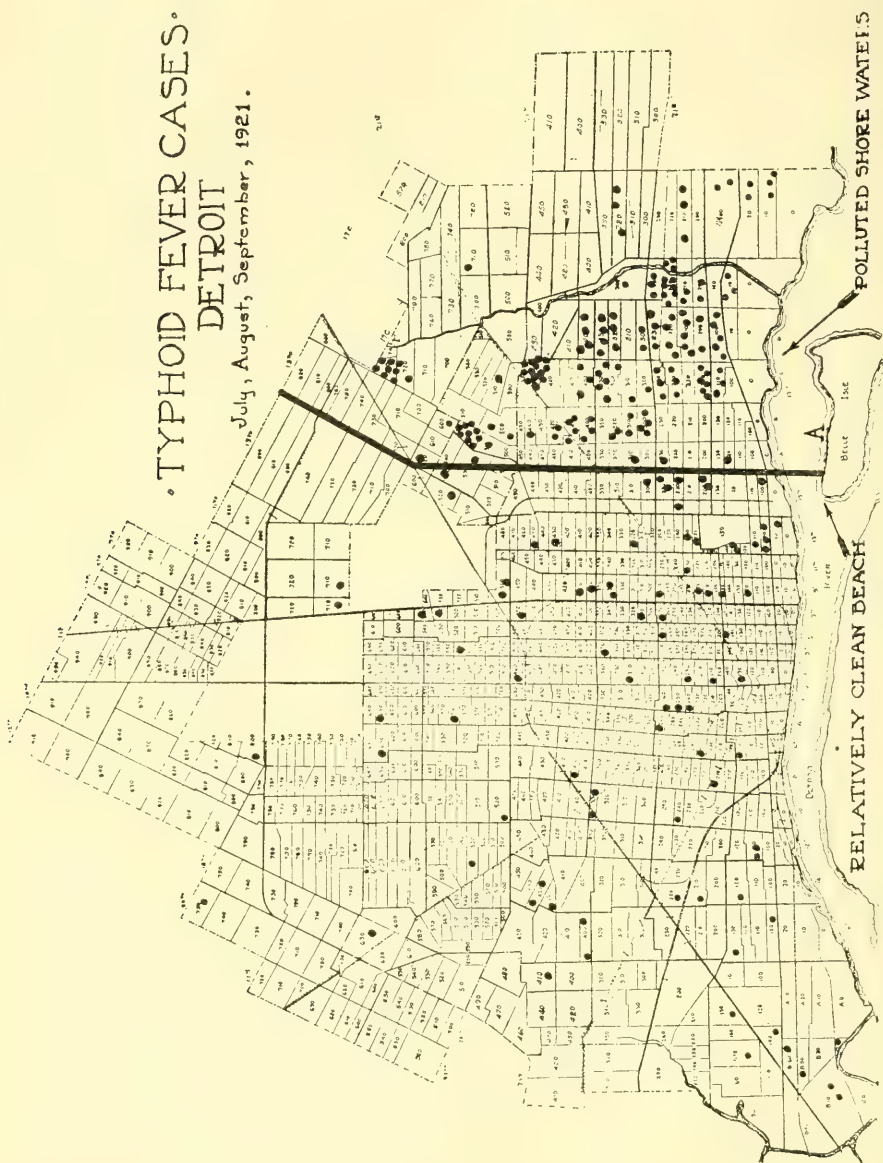
On some of the smaller boats pressure filters are employed. These, however, are not suitable for large supplies, and give a low degree of bacterial efficiency, and consequently may become a source of actual

danger. Ozonization has had its advocates, but is very uncertain of results, as well as expensive in operation. Liquid chlorin has been given a general trial, but found dangerous, due to possible leakage in connections, liberating thereby the gas, which may be absorbed only by flooding the engine room with water. No satisfactory means of automatic control has been devised for such a chlorin plant. Ultraviolet ray sterilization and steam offer at the present time the best results. The former is most generally used on passenger ships on our Great Lakes—the latter on the freighters. The ultraviolet ray must be employed in connection with a pressure filter, as the water must first be freed of large organic particles and sediment, since the light cannot penetrate such obstacles. When first employed, a gravity type of ultraviolet machine was used, but this has now been superseded by a more satisfactory pressure type. This method, although more expensive than steam, due to the possible breakage of lamps, has proved very efficient and gives great promise for the future. Steam sterilization automatically controlled by valves proves satisfactory with certain types of water. When lime is present the valves tend to become hardened and fail to work. Cooling is accomplished by recirculating the effluent through coils placed inside of the incoming water. In lakes where the water is generally warm, it is difficult to obtain a rapid cooling of the treated water, with the result that the bacterial count remains high, due to aftergrowths. This difficulty is met with on the Great Lakes during the hot summer months. Brine pipes can be used, but this again adds to the cost, and most lake boats are not equipped with such apparatus.

In discussing the relation between boats and typhoid fever, it may be well to call attention to the fact that these transports may infect city supplies; in fact, this is exactly what did happen in 1890 at Sault Ste. Marie. The sewage of boats is discharged untreated into the water. It has been suggested that with the abundance of steam at hand it would not be a heavy financial burden upon the owners of boats to compel them to sterilize all waste material before discharging it into the water.

Of the millions of people traveling daily on our railroads there are many who are typhoid carriers; some are in the initial stage of the disease; some are convalescing; while others are either temporary or permanent carriers. The fecal discharges from these people are being scattered along the railroad tracks, some of it to be washed into public water-supplies. This is a condition for which no satisfactory remedy has been found. Several devices have been offered, but none has proved satisfactory. Here is a matter awaiting the discovery of suitable apparatus by some engineering genius. The drinking water used on interstate trains is under the supervision of the U. S. Public Health Service.

These waters are periodically examined, generally by some state or municipal board of health. The common drinking cup on railroad trains has disappeared. There is some carelessness still in filling both



the water and the ice tanks. The water-supplies of those trains which are confined to individual states are under the supervision of the State Board of Health.

To acquire typhoid fever from water it is not essential that the water be used for drinking purposes. Of course, some of it must reach the mouth and be swallowed. There are several cases on record, when in the midst of a municipal or village epidemic, some more than usual intelligent family stops drinking the water, but continues to use it in cleaning the teeth and in complete or partial ablution of the body. The possibility, as indeed the probability of acquiring this disease by bathing in infected pools, should not be overlooked. Articles of food which are eaten raw may be washed with infected water and the disease thus transmitted.

Typhoid fever may result from bathing or swimming in grossly polluted waters. The accompanying map illustrates the conditions which obtained in Detroit during the unusually warm month of July, 1921. The municipal bathing beach is on Belle Isle, at the point marked "A." This island park is connected with the mainland by a bridge, the latter terminating in a boulevard which divides the western and central section of the city from the eastern, and tends to direct the westerly traffic to the Belle Isle beach, while it was found that the residents of the eastern section were in the habit of dressing at home and traveling to the nearest beach. The river current is swift, and the island shore is sanitary, while the waters bordering the mainland are highly polluted with sewage discharged into the river from two small streams above. This outbreak of typhoid fever was ascribed to river bathing only after all other possible sources of infection had been eliminated, and after it had been definitely found that the people in this particular section of the city were accustomed to bathing in these polluted waters.

It is worthy of observance that the most notable improvements in water-supplies have been due to our esthetic sense and desire for the comforts of life rather than for the purpose of preventing disease. The drinking of polluted water is, fortunately, naturally repugnant to man. One might speculate as to what would have happened to the race had man been an obligate water drinking animal. The senior author has been severely taken to task for saying that infected water has killed more people than alcoholic drinks. The statement is true, however, but it should not be considered as a recommendation for alcoholic drinks but as a condemnation of infected water. We are inclined to the opinion that the preparation and consumption of alcoholic and caffein-containing drinks have been due largely to an unconscious effort on the part of man to escape infection by water-borne diseases. For centuries the surface water-supplies of central and southern Europe were almost universally and continuously infected, but a large portion of the people escaped typhoid fever because they did not drink water. For many years, and even now, the waters of rural France and Belgium

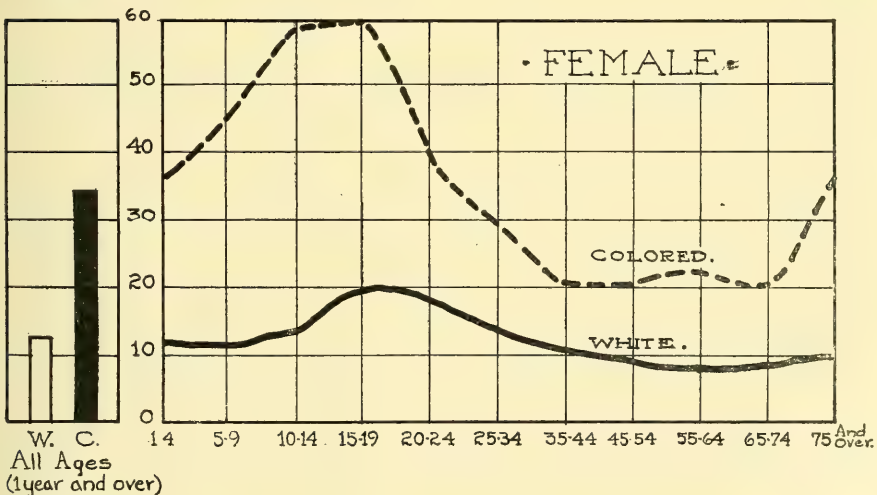
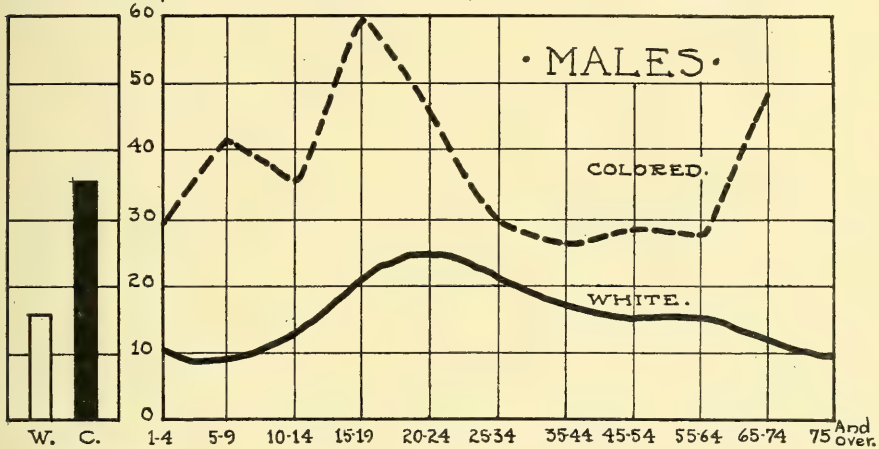
may be regarded as contaminated. It is true that all rural Frenchmen have not died from typhoid fever, but they have not as a rule drunk water. Enough of them diluted their native wine with water, sufficiently so that the mixture had no destructive action on the bacillus, drank it, and acquired typhoid fever. The dejections from these, un-disinfected, were deposited in shallow privies or thrown on the surface and reached the water-supplies. Thus the vicious circle was established and continued to operate from generation to generation. Before Pettenkoffer's time, the people in Munich who drank water developed typhoid fever and many died. The more sensible people brewed their beer and did without water. Unconsciously, it happened that the people of those localities most heavily infected with typhoid fever turned to some other drink than water. The Chinese have kept relatively free from this disease by their universal addiction to tea drinking, for in the preparation of this beverage sterilization of the water is secured. The introduction of municipal water-supplies was not for the purpose of preventing disease but with the intention of making life more comfortable. The engineer of ancient Rome showed skill in the construction of his great aqueducts, which still are used in part in conveying pure water to the city. These works must have cost much in time, labor, and money, but the Roman citizen enjoyed his bath more than he feared infection. His esthetic sense was thrilled by the play of the great fountains and he had never heard of water-borne typhoid fever. The introduction of an abundant water-supply into Rome necessitated the disposal of the excess of water, and as a consequence the Cloaca Maxima and other sewers were completed. Had man been an obligate water drinker, in our opinion, one of three things would have happened. (1) He would have been exterminated by water-borne diseases. (2) He would have secured immunity to these diseases as have most of the lower animals. (3) He would have continued to be a nomad, moving constantly, fleeing as it were, from the localities which he contaminated with his own excretions. It should not be understood that these statements are made for the purpose of recommending the continuation of the use of any of these artificial beverages. For this country at least enough safe water can be found so that resort to alcoholic drinks is no longer necessary. However, we wish to state with just as much emphasis, that, in our opinion, to condemn the use of wine in France, Italy, and other vine-growing countries would at this time be both unscientific and inhumane.

It may be remarked that the year 1921 has shown a slight setback in the typhoid situation which is quite general. This is revealed in the reports of the Metropolitan Life Insurance Company from its millions of policies among wage earners throughout the United States. The

typhoid death rate among this class was 6.6 per 100,000, or about the same as 1920. However, during the latter half of the year the rate was actually higher than during similar months of the preceding year.

TYPHOID FEVER MORTALITY BY COLOR AND SEX.

Death rates per 100,000 Persons exposed 1911 to 1916 inclusive.



Experience of Metropolitan Life Insurance Company. Industrial Dept.

Fig. 22.

From January to June there was a decline of 14 per cent in the typhoid death rate among white persons and 15 per cent among colored persons, as compared with the rate for the first six months of 1920. The num-

ber of deaths during the latter part of the year, however, exceeded those of 1920.

TABLE XVI
TYPHOID FEVER MORTALITY,
ANNUAL RATE PER 100,000
INDUSTRIAL DEPT., METROPOLITAN LIFE INSURANCE CO.

	1921	1920
July	7.2	5.6
August	10.3	6.7
September	13.6	6.7
October	8.4	10.7
November	8.7	6.7
December	6.0	5.0

We quote from the Metropolitan Statistical Bulletin of February, 1922:

"The best explanation that we can offer for the cessation in the fall in the death rate was the unusual temperature conditions of 1921. The year was characterized by a world-wide excess of heat and deficiency of rain. In New York City, for example, there was an excess of 1,046 degrees of temperature above normal and the rainfall was 10.25 inches less than the average for a long period of time. The shortage of rain was constant over most parts of the United States and over the world. It was responsible for droughts in many places. The water-supply was consequently lowered to the danger point in many cities. Therein probably lies the explanation for the increased typhoid fever rate for the last half of 1921. For, with lowered water-supplies, there was immediate need for access to impure and discarded sources, where there were no adequate facilities for the requisite treatment which would insure safety."

Detroit experienced a sharp outbreak of typhoid during August, 1921, which was believed to be due to bathing in polluted shore waters. This is discussed elsewhere.

Milk-Borne Typhoid.—Milk may become infected with typhoid bacteria by its dilution with infected water, by washing milk cans with infected water, and by coming in contact with infected persons or infected things. Ordinarily, typhoid bacilli do not multiply rapidly in water. Experimental results show that these organisms live longer in sterilized or distilled water than they do in water which is rich in putrefying organisms. In the latter instance the saprophytic bacteria overgrow and destroy the typhoid organisms. On the other hand, in milk, typhoid bacilli find an excellent medium for their multiplication. For this reason the protection of milk supplies has become an imperative sanitary procedure. It is essential that all dairy workers should observe the most rigid personal cleanliness. The udder and adjacent parts of the cow should be thoroughly cleansed before milking. It will be understood that there is no danger of milk infection directly through the animal. Cows may drink typhoid-infected water or they may eat food infected with these bacilli, but the milk as it comes from the udder

will not be contaminated by this organism. On the other hand, any part of the exterior of the animal may carry the infection after wading in filthy water or resting upon grass polluted by typhoid discharges from man. For these reasons both the milch cow and the person who draws or handles the milk must not carry typhoid bacilli and should be kept scrupulously clean. All milk vessels should be sterilized. Likewise, they should be screened from flies. The milk supplies of all well-regulated cities are frequently inspected and scored to prevent the introduction into this essential food of any infective material. Due to the fact that typhoid bacilli multiply rapidly in milk and that the milk from different animals and often from different herds, is mixed before distribution, this article of food becomes an important factor in the spread of the disease. For these reasons inspection of dairies and of dairy workers is not sufficient to protect the consumer. When milk does become infected with typhoid organisms and the disease is spread through this medium, it is, as a rule, not less than ten days before the outbreak manifests itself. During this time hundreds of people may have been infected. Most cities require that all milk be either pasteurized or certified. Of these procedures pasteurization is the one of choice. Sterilization of milk destroys its vitamins and thus renders it a less desirable food. In the last two decades of the nineteenth century the sterilization of milk was generally employed by the more intelligent people. Infants were fed for months, and some for years, largely if not solely, on this food. It was found that some of these developed scurvy and other evidences of malnutrition. The conclusion was reached that these untoward results were due to sterilized milk. Then there followed a time when certified milk was greatly in demand. A certified milk is one which has been examined by a bacteriologic expert and found not to contain bacteria of any kind in excessive numbers and which has been produced under such conditions as reasonably assure the absence of all pathogenic organisms. To secure safe certified milk, expert skill is demanded and this must be in operation at all times to secure satisfactory results. At the present time pasteurization of milk is the cheapest, simplest and most effective process for preventing milk-borne epidemics. The city which does not require the pasteurization of all milk, with the exception of that certified, sold within its limits can hardly be said to be modern in its sanitary service. Milk epidemics of typhoid fever have for the most part been easily traced but, as a rule, not until many families have been infected.

The location of cases in milk epidemics is characteristic, for they will be found to occur, for the most part, along the single milk route affected. In water-borne typhoid the cases will be found fairly evenly

distributed over the city, or proportionate to the population served by the water mains.

A most interesting report of a milk borne epidemic is that given by Bowen, epidemiologist of the New Jersey State Board of Health, in the Annual Report for 1912. Cases began to appear in Moorestown, N. J. (population about 4,000) about July 28. Suspicion was first directed to the water-supply because it had not been of satisfactory character for some time. However, on looking into the matter more closely

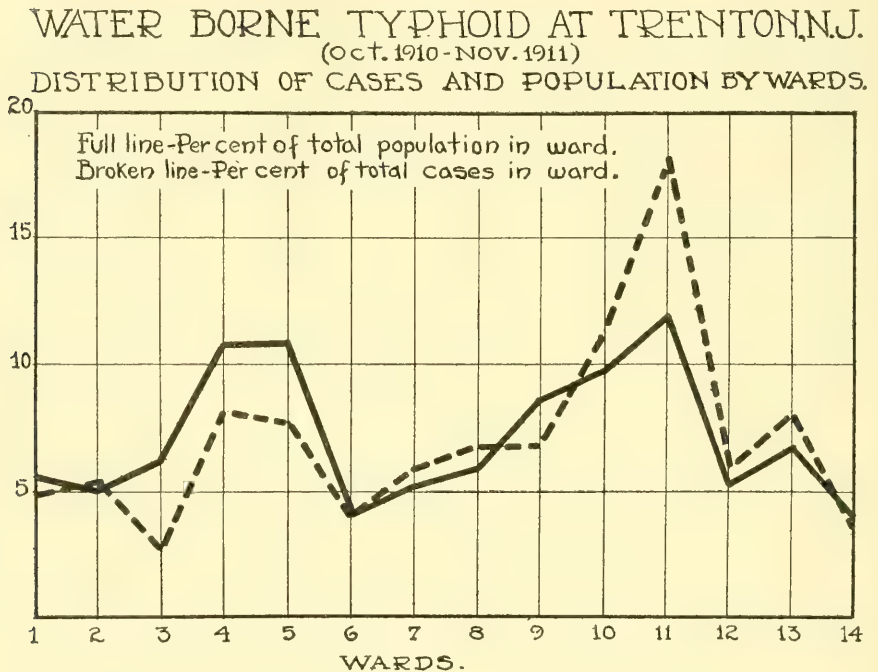


Fig. 23.

it was soon discovered that cases were largely confined to families supplied with milk by dealer M. H. In fact 47 of the 53 cases included in the entire outbreak were related to one dealer who supplied only about one-half of the milk sold in town.

MILK DEALERS	DAILY AMT. SOLD	NO. OF CASES AMONG PATRONS
M. H.	700 Quarts	47
D. R. Farm		
Supplying M. H.	50 Quarts	6
H.	600 Quarts	0
S.	50 Quarts	0

Furthermore, the cases were confined to those families which received milk in quart bottles. Those receiving only pint bottles had no typhoid.

Cases in families receiving quart bottles only	27
Cases in families receiving quart and pint bottles	15
Cases in families receiving pint bottles only	0
Cases at Seaside Park	5
Cases on the farm	6

Another fact of epidemiologic interest was that of the 42 cases in the town proper, 33 occurred on Route No. 2 and only 9 on Route No. 1 of M. H's supply.

People of all ages and occupations were included among the cases. Thus 13 were under 10, 11 from 10 to 20, 15 from 20 to 40, 8 from 40 to 60 and 6 over 60.

The chronology of the cases is shown in Table XVII.

TABLE XVII

DATE	NO. OF CASES SHOWING ONSET
July 20	4
21	0
22	3
23	2
24	1
25	1
26	2
27	6
28	1
29	1
30	4
31	5
August 1	3
2	0
3	2
4	0
5	5
6	2
7	2
8	2
9	0
10	3
11	1
12	2
13	0

The causal circumstances as worked out in this study were as follows: On July 13 and 14 the manager of the D. R. farm had been con-

fined to the house with an illness which was judged at the time to have been a slight attack of grippe, supposedly resulting from exposure while at work in the fields during a storm. He was visited and prescribed for by two different physicians. Feeling somewhat better, he again resumed his farm duties. On July 29 two cases of typhoid were reported at the farm, one in the person of a farm hand and assistant dairyman who lived in the family of the farm manager, and the other in the wife of the head dairyman, who resided in a tenant house on the farm. The onset in these two cases was about July 20. About August 1 the head dairyman showed suspicious symptoms, and he, with the two other sick persons, was removed to a hospital.

On August 6 a specimen of blood from the farm manager gave a positive Widal, and on August 14, typhoid bacilli were isolated from his feces. The manager's wife and two of his five children were later stricken. Investigations on nine other farms contributing to M. H.'s supply revealed no suspicious carriers. There were five persons working in the milk depot of M. H. The senior member of the firm had had typhoid twelve years previously, but on August 6 he gave a negative Widal. Specimens from the other four on August 7 showed two more positives, the junior member of the firm and his son. Within a day or so later the son was in bed, but the father kept on working although admittedly feeling ill. He was then removed to a hospital, and both father and son had severe cases of typhoid. The original infection of the milk supply was due to the farm manager. It was learned that he frequently defecated during the day in places where no suitable toilet paper was available and that the milkers did not always properly clean their hands before milking. We have previously stated that all infection was confined to those receiving quart bottles and most cases were on Route 2. It seems that the D. R. farm contributed about 160 quarts of M. H.'s total supply of 700. From 30 to 40 quarts of the morning's milk from the D. R. farm were separated shortly after its receipt at the milk depot. This milk furnished nearly all the cream sold to local dealers. The remaining portion of the morning's milk was put up in pint bottles. There was no typhoid among families using pint bottles only. This fact, with other supporting data, excluded the morning milk as a source of infection. The night milk from the D. R. farm was all put up in quart bottles at the milk depot of M. H. Twenty-one quarts of this went to families in Seaside Park, where there resulted 5 cases of typhoid. The remainder was delivered in Moorestown. The wagon traversing Route 2, on which the majority of cases were located, was in charge of the junior member of the firm, and it was this wagon which received most of the night milk from the D. R. farm. The methods of handling milk in the depot were designed to avoid mixing the

milk from different farms. The bottling machine was entirely emptied of one batch before another was added. When loading the wagons the quart bottles of night milk from the D. R. farm were most likely to be placed on the wagon which covered Route No. 2. Thus Route 1 was getting the greater proportion of milk from other farms. While the manager of the D. R. farm usually assisted in the morning milking, he did on occasions assist with the night milk, and as this milk was stored overnight, there was an opportunity for the typhoid bacilli to increase in numbers, whereas the morning's milk was delivered immediately to the depot. It is the supposition that the manager unconsciously infected the night milk supply.

It is important to note in connection with this outbreak that the D. R. milk was obtained from high priced cows, part of which had been tuberculin tested. The dairy scored high, and the milk was regarded as of superior quality. Cans and utensils were subjected to flowing steam after washing, and yet, in spite of these precautions, the milk itself was infected probably by dirty hands in milking. The sale of milk from the D. R. farm was stopped on August 2. On August 6 business was temporarily suspended at the M. H. milk depot until all equipment was thoroughly sterilized, and furthermore, all milk was heated to 145° F. for 20 minutes before being distributed. Following the sickness among workers in the milk depot on August 7, the M. H. dairy was required to stop all sale of milk on August 8. They continued distributing, however, securing a supply of pasteurized bottled milk from an entirely new source. The onset of the final case was on August 12, or 10 days following the stoppage of milk from the D. R. farm.

Inquiry among 43 of the 53 typhoid cases showed that the outbreak had cost Moorestown nearly twelve thousand dollars divided among the following items.

1. Money loss in wages or other earning power of 15 wage earners during illness	\$ 2,264.46
2. Cost of drugs and medical supplies in 22 home-treated cases	385.24
3. Paid for nurses' salaries, in 18 cases	2,885.50
4. Maintenance of nurse (board, etc.)	691.50
5. Attending physicians' bills in 24 home-treated cases	1,903.94
6. Attending physicians' bills in 7 hospital cases	455.50
7. Other expenses incident to illness	1,250.42
8. Loss of wages of members of families in nursing three patients treated at home	94.00
9. Paid for hospital treatment, 9 cases	1,092.00
10. Cost of hospital treatment in ten charity patients	645.00
Total	<hr/> \$11,667.56
Total time lost by reason of illness	366 weeks, 6 days
Days patients spent in hospitals	758

In 1908, Trask, of the U. S. Public Health Service, collected reports of 179 milk-borne epidemics. This number might be increased greatly if the investigation were brought up to date. In 1917 Frost, of the same service, made a study of typhoid epidemics in all cities of more than 10,000 inhabitants on the Ohio River watershed. Excluding Pittsburgh, Cincinnati, and Louisville, Frost's records covered 25 cities of over 25,000 inhabitants each, with an average aggregate population during the period from 1910 to 1914 inclusive of slightly more than 1,600,000. During the five years mentioned, distinctly milk-borne outbreaks of typhoid fever, totaling 446 cases, were reported in seven of these cities. Milk was believed to be the cause of approximately 5.4 per cent of all reported cases. Approximately fifty per cent of the milk sold in 20 of these cities was pasteurized at the time of the survey, about forty per cent by the "holding" system and about ten per cent by the so-called "flash" methods. Frost concludes that the number of cases of typhoid fever which actually occurred in these cities during the five years was about 24,000, and that milk was responsible for approximately two per cent of the total cases. Lumsden, of the same service, made a study of the prevalence and causes of typhoid fever in the District of Columbia from 1906 to 1909 inclusive. During 1906, 1907, and 1908, Lumsden concluded that about ten per cent of all the cases originating in the District of Columbia were due to milk infection. Levy, in a study of 2,300 cases in Richmond, Va., could find no evidence of an epidemic due to milk contamination. Freeman, reporting for the state of Virginia for six years in a total of 12,000 cases of typhoid fever, could find only 100 attributable to milk infection. It must be evident that the part played by milk infection in the causation of typhoid fever varies greatly in different places and at different times. It is relatively easy to ascertain, or at least to approximately estimate the influence of an improved water-supply upon typhoid fever death rates, but it is much more difficult to get anything like an exact estimate of the typhoid fever due to milk supplies. The change in water-supply comes suddenly, while improvements in milk-supply are more gradual. Occasionally it happens that a city demands that on a certain date all milk sold within its limits shall be pasteurized. This occurred in Cincinnati on the first of July, 1914. However, we are without data concerning the effect of this radical improvement on typhoid fever in that city, neither do we know how effective the city ordinance became on that date. A similar ordinance went into effect in Detroit in May, 1916, since which time there has been no milk-borne epidemic in that city; whereas prior to that time, although fifty per cent of the milk had been pasteurized, such outbreaks were of annual occurrence. There is still another factor which remains of uncertain value in trying to make this

estimate. This concerns the efficiency of the pasteurization method employed. Simply ordering that all milk be pasteurized does not secure the efficient employment of this process.

According to an announcement of the U. S. Department of Agriculture in January, 1922, there is not a city over 75,000 inhabitants but that has pasteurization for a portion of its supply. In the cities over 500,000 all have more than 50 per cent of the milk pasteurized. In the cities from 100,000 to 500,000 at least 90 per cent report more than 50 per cent of the supply pasteurized. In the cities from 75,000 to 100,000 the percentage is 73. It is the smaller communities that are behind in this matter, but even here the improvement in six years' time is marked. Thus in 1915 in communities between 10,000 and 25,000 only 6 per cent had more than 50 per cent of their supply pasteurized. In 1921, 33 per cent of cities were in this class.

There is no pasteurization whatever (1921) in 14.7 per cent of the cities from 50,000 to 75,000; 11.3 per cent of the cities from 25,000 to 50,000 and 38.9 per cent of the cities from 10,000 to 25,000.

Contact Typhoid.—When the Typhoid Commission began its investigation into the prevalence of typhoid fever in August, 1898, it had no thought of finding the disease to be spread by any other means than contaminated water or milk. Indeed, it was well-nigh the universal belief of epidemiologists at that time that this is essentially, if not exclusively, a water-borne disease. The commission proceeded first to Camp Alger, Va., where the Second Army Corps had begun assembling early in May. There was nothing in the topography of the camp which indicated that the location had been unwisely selected. The average elevation of the regimental camp sites above the Potomac River is about 300 feet. The general surface is decidedly undulating, being well provided with open spaces for regimental or brigade encampment and interspersed with native forests. The location is traversed by a few small brooks and provided with a number of shallow springs. The latter, however, were not used except by small organizations and for a short time, during which there was little or no typhoid fever. The layer of soil is quite thin and is underlaid by a stratum of impervious clay extending down towards the rock, being separated from the latter by a layer of quicksand. The water-supply furnished the soldiers was obtained by driven wells carried through the clay into the sand. Early in the formation of the encampment there was some delay in securing an abundance of safe water. One or more of these driven wells supplied each regiment. The water from the wells was soft, clear, and palatable. At the request of the commission samples of water from many of these wells were carried to the Army Laboratory in Washington and carefully examined, both chemically and bacteriologically. These analyses

failed to reveal the presence of great numbers of bacteria or of any pathogenic or toxicogenic organism. There were 18 regiments with a mean strength of 19,807 at Camp Alger. Among these there were 2,226 cases of typhoid fever with 212 deaths. The commission during its six days at Camp Alger made arrangements for the sterilization of all water and proceeded to Jacksonville, Fla., very much in doubt about the typhoid fever at Camp Alger being water-borne. It may be stated here that the Second Army Corps was moved from Camp Alger soon after this inspection to Camp Meade, Pa. Typhoid fever accompanied the corps in this transfer, and although the mean strength was reduced to 13,962, the number of cases in the six or eight weeks at Camp Meade was 2,690, with 150 deaths.

At Jacksonville, Fla., where the Seventh Army Corps was located, the water-supply was the same for the city and the camp. It came from four artesian wells varying in depth from 630 to 1,020 feet. The water contained sulphureted hydrogen, which was entirely dissipated by aeration. These wells were located between the city and the camp. Pipes carried the same supply in one direction to the city and in the other direction to the camp. The population of the camp and that of the city was each in round numbers 30,000. Both civilians and soldiers drank water from the same source. There were only a few sporadic cases of typhoid fever in the city at a time when each of the three division hospitals was receiving a score or more of patients with this disease each day. Evidently the typhoid fever in the Seventh Army Corps could not be water-borne unless the water became infected after leaving the city water works.

At Chickamauga, Ga., the First and Third Army Corps had been assembled in May. Undoubtedly there was some water-borne typhoid in this camp. The intake pipe for the camp supply had been located so near the junction of Chickamauga Creek with the Cave Spring Branch, which drained many of the camps, that it hardly seems possible that the piped water wholly escaped contamination. However, that even at Chickamauga infected water was not the chief factor in the spread of typhoid fever, is shown by the fact that regiments which did not drink piped water became widely infected with the disease; and it is further demonstrated by the fact that the spread of typhoid fever continued after the regiments had been moved to Knoxville, Tenn., and Lexington, Ky., at both of which places the water-supply was above suspicion. In addition to the contamination of the piped water at Chickamauga there is evidence that some of the wells in the park, and some of the springs both within and outside the park, became specifically contaminated. Long before the commission finished its round of camp inspection the evidence that polluted water had been a relatively un-

important factor in the dissemination of the disease was overwhelming. In the camps studied by the commission there were all told 92 regiments consisting of 107,973 officers and men. The total number of cases of typhoid fever occurring among these during less than four months was estimated by the commission to be 20,738. This is equivalent to 19.26 per cent. While the commission was being forced to conclude that the disease was not disseminated largely by water, the avenues through which it was disseminated plainly revealed themselves. Before considering the newly revealed methods of dissemination, it may not be amiss to briefly mention some of the theories proposed at that time. There were many intelligent medical officers who believed that some intangible local condition, inherent in the place, was an important factor in the development and continuance of the epidemics. There is apparent in man a tendency to believe in the evil genius of localities. He is prone to attribute many of his misfortunes to indefinable conditions surrounding the place in which he has suffered. This is the old miasmatic theory of the causation and spread of disease. While inspecting the First and Third Army Corps, members of the commission were told that the word "Chickamauga" means "river of death," and that the fever prevalent in the park was neither typhoid nor malaria, but "Chickamauga fever." Like evidence of belief in the evil genius of locality was manifest in other camps.

Some were decidedly of the opinion that the camp epidemics were due to the fact that large numbers of men from the northern states had been assembled in the South and had not become acclimatized. However, the Fifteenth Minnesota first developed typhoid fever at the Fair Grounds at St. Paul. There was certainly no evidence that any evil climatic influence was connected with this place. The regiment carried the epidemic with it to Fort Snelling, which had long had the reputation of being one of the most healthful army posts in the United States. From Fort Snelling the Fifteenth Minnesota was transferred to the open fields of Camp Meade, where generations of Pennsylvania farmers had passed the average number of years allotted to man without suspecting that their country was an unhealthy one. Typhoid fever continued with the command from Minnesota because the men carried the germs of the disease in their bodies, clothing, bedding, and tentage. Certainly any rational being would prefer any of the above mentioned localities to Port Tampa as a place of summer residence, and yet there was not a regiment in the Fourth Army Corps in camp for so long a time in Florida that had as many cases of typhoid fever as did the Fifteenth Minnesota which had never crossed the Mason and Dixon line.

The old pythogenic theory of Murchison was revived and to a superficial observer had much in its favor. Translated into the terms of

modern medicine, this theory is that the colon bacillus may undergo a ripening process by means of which its virulence is so increased and altered that it may be converted into the typhoid bacillus, or at least may become the active agent in the causation of typhoid fever. Many French, English, and American Army medical officers believed that typhoid fever may originate in this way. Rodet and Roux of the French Army stated the belief that outside of the body the colon bacillus acquires a "typhogenic" property. Davies, assistant professor of hygiene in the English Army Medical School, expressed his belief in this theory. Many American medical officers gave it their adherence in 1898. The best statement concerning this theory about that time was made by Davies, and from it we make the following quotation:

"It is well known that 'camp diarrhea' is of the commonest occurrence among troops shortly after taking the field in a tropical or subtropical climate. Change of habits, change of food, improper or unsuitable food, bad water, heat, and exposure to sun and chill—these are all obvious factors in its causation; there is nothing in any way specific. Let's consider the sequel as regards the individual and as regards his surroundings. The individual may in some cases remain in fairly good health and vigor in spite of a continuance of the bowel trouble; other individuals may suffer more from the exposure, fatigue, and weakening effects of the continued flux. The surroundings may possibly be and remain sanitary, the camp clean, the water pure; but in all probability the reverse will be the case—at any rate, in some instances—the water bad, the soil fouled, very likely overcrowding of the camp, with consequent difficulty if not impossibility, of proper removal or disposal of fecal matter. Under certain conditions of heat and moisture, favorable to the development and multiplication of low forms of vegetable and animal life, which is the more likely or reasonable to expect, that diarrhea in weakly and exhausted individuals should remain diarrhea and nothing more, or that with an increase of filth and decomposition, polluting soil, air, and water, a development of filth generated pythogenic poison should take place, capable of causing in such weakly persons a fever with diarrhea, a poisoning of the organism, producing pyrexia and inflammation of certain glands in the alimentary tract—in fact a specific fever? Is this supposition of the evolution, gradual or rapid according to circumstances, of a disease poison, dependent on increased conditions of pollution of soil, air, or water, either separately or all three together—unreasonable or illogical? Would it not, on the contrary, be more unreasonable to suppose that, under such conditions, there would be no evolution at all? These conditions of camp pollution undoubtedly exist and tend to increase in many instances. Are they to have no effect? Is diarrhea to continue as simple diarrhea, or is evolution to come into action and produce a new disease? New, indeed, only because the causes necessary for its production are just now brought into action—spontaneously only in the sense that water is of spontaneous origin, when from hydrogen and oxygen the electric spark has produced water where no water was before."

If opportunity were ever given for the colon bacillus to develop into the typhoid bacillus and cause typhoid fever, such opportunity certainly existed in the camps inspected by the Typhoid Commission in 1898. Camp pollution could scarcely have reached a higher degree of uni-

versal prevalence than was the case in Chickamauga Park. Latrines were frequently overflowed by heavy rains and their contents distributed on the adjoining surface. Fecal matter was deposited not only in the latrines but behind every tree and bush. One could not walk from one regimental organization to another without soiling the feet with fecal matter. The colon bacillus had every conceivable opportunity to ripen into something more malignant. It could develop in wet or dry places, under the earth or on the surface of the earth, in the shade or in the sun. The whole of Chickamauga Park was strewn with human manure.

The following extract is from a report made by Captain Bevans of the Fifth Illinois Volunteer Infantry as to the condition of the camps occupied by that regiment. This regiment was assembled at Camp Tanner, Springfield, Ill., from April 26 to May 14, 1898. The water-supply was from the city mains and was good. The regiment occupied cattle sheds and stables, and sheep pens and neighboring hillsides were used as privies. Finally, sinks were dug but these soon became filthy in the extreme. On arrival at Chickamauga, May 15, 1898, this regiment was encamped in a place which had been previously occupied by troops. There were old sinks, partly filled, scattered over the site. Tents were pitched over places where sinks had been. Owing to the character of the soil it was difficult to dig latrines. It was still more difficult to obtain efficient guards for the latrines. There was no regular systematic inspection from a higher source than the regiment. About the middle of June, Bevans was detailed for duty at the First Division Hospital of the First Army Corps. Here the sinks were always neglected. This was due largely to an insufficient number of orderlies for the care of the sick. Much time was wasted in carrying out conflicting and confusing orders. An attempt was made at the disinfection of bedpans used by typhoid patients, but the sinks were allowed to fill and overflow without attempt at policing. On July 28, this regiment was moved to Newport News. Here the camp was small and the sanitary condition was greatly improved, but typhoid fever continued. From Newport News this regiment was sent to Camp Meade, where it arrived August 17. The surgeon says:

"After the lax regulations and inspections to which I had been accustomed in other camps, the supervision as to sanitary matters at Camp Meade seemed almost tyrannical. There was constant, thorough, systematic inspection from sources higher than the regiment. A sufficient number of guards was provided to watch every sink, and each soldier was compelled to cover his own fecal matter, spades being provided for the purpose. Specific orders were issued as to the use of water and filters were provided for all. Cooperation of commanding officers in sanitary matters was insisted upon. The slightest neglect in carrying out sanitary regulations in force at the camp was followed by immediate reprimand of the officer at fault. The condition of the camp was excellent."

The above is a statement without exaggeration of the conditions which

existed in the majority of the camps from the initial state encampment to the final dissolution of the organization.

Notwithstanding the almost universal soil pollution, no case of typhoid fever originated *de novo*. The pythogenic theory proposed by Murchison was conclusively controverted by the Typhoid Commission of 1898. It was shown that the specific bacillus of typhoid fever was introduced into every one of our state and national encampments. The commission ascertained the first case or cases in every organization, regiment, and company, and traced the spread of the disease from comrade to comrade, from tent to tent, and in some instances from organization to organization. There could be no doubt from the evidence accumulated that the greatest factor in the spread of typhoid fever in our camps in 1898 was contact or comrade infection. It was found that in a general way the number of cases of typhoid fever in the different camps varied with the methods of disposing of fecal matter. This was well illustrated in the three divisions of the Seventh Army Corps. The First Division was most uncomfortably located at Miami, Fla., from the last week in June until the second week in August. On the last mentioned date it was removed to Jacksonville, where it joined the other divisions. During a part of its stay at Miami and during the entire period of its encampment at Jacksonville, water carriage was employed for the disposal of fecal matter. The number of cases of typhoid fever that developed in the six regiments of this division was 1,030. In the Second Division the tub system of disposing of fecal matter was employed. By this method infected fecal matter was scattered all through the camp. The number of cases of typhoid fever that developed in the nine regiments of this division was 2,693. In the Third Division regulation pits were used for the disposal of fecal matter. The number of cases of typhoid fever in the seven regiments of this division was 1,292. The tub system of disposing of fecal matter was regarded as the most unsatisfactory and was condemned. The regulation pit system was found to be unsatisfactory for several reasons. In the first place, on account of geological formation, pit latrines may be difficult of construction and unsatisfactory in operation. At Chickamauga the rocks are near the surface and are covered by a clay. The latter when thrown out in digging hardens in the sun, and when thrown back into the pit on the fecal matter has but little absorptive power. At Tampa it was impossible to use pit latrines on account of the height of the ground-water. The commission recommended that wherever water carriage could not be secured all fecal matter should be disinfected, carted away from the camp and buried.

Had an attempt been made to disseminate typhoid fever it would have been difficult to have devised more efficient methods than some of those

employed in our camps in 1898. At Chickamauga for a while it was customary to detail from one or more commands 100 or more men from the line every morning. These men went to the hospital, handled bed-pans used by persons sick with typhoid fever, and at night returned to their comrades. Most of these men were wholly ignorant of the nature of infection and the methods of disinfection and no adequate instruction was given them. At one of the division hospitals the members of the commission saw orderlies of this kind come from the hospital and partake of their midday meal without even washing their hands. These men handled not only the food which they ate, but passed articles to their neighbors. This is an illustration on a large scale of infection from the hand by way of the food to the mouth. This, so far as we know, is the first time that attention was called to the necessity of the sterilization of the hands of those who handled food. These orderlies, however, undoubtedly disseminated typhoid not only in handling food, but by transferring specific bacilli from their hands to the clothing worn by themselves and that of their comrades, to the blankets used by themselves and comrades, and to the tentage sheltering the group. The commission found that certain tents were badly infected, the majority of their inmates developing the disease, while other tents wholly escaped. Blankets and tentage became soiled with typhoid discharges and in this way the disease was propagated and carried by the company wherever it went. The commission estimated that of all cases of typhoid fever 62.80 per cent were due to comrade or contact infection. Studying the spread of the disease by tents, most striking results were obtained. It often happened that the majority of those in one tent would acquire the disease before it was recognized in any other tent in the company. From the first tent the disease would spread to the men not necessarily in the next tent, but to those who came most intimately into contact with the occupants of the infected tent.

The investigations of the Typhoid Commission demonstrated that typhoid fever is not only an infectious, but also a contagious disease; that it may be transferred from one person to another by contact, and that the clothing and bedding of typhoid patients should be disinfected with as much care as is given to these matters in case of diphtheria or scarlet fever. It was not until the clothing, equipment, blankets, and tentage of our soldiers were disinfected in 1898 that typhoid fever was arrested.

As has been seen, the surface of Chickamauga Park, especially where strips of wood existed, was frequently dotted with fecal deposits. At the time of the inspection of the Third U. S. Volunteer Cavalry it was impossible to walk through the woods near the camp without soiling one's feet with fecal matter. Much of this was probably specifically infected, and there can be no doubt that this infection was carried by

the men into their tents where more or less of the infected matter was transferred to blankets and tentage. Contact typhoid fever may be either direct or indirect. The commission estimated that 35.01 per cent of the contact cases were due to direct contact, while 27.79 per cent were due to indirect contact, making of contact cases 62.80 per cent, as has been stated, of all cases. It may be said parenthetically that notwithstanding the fact that these findings were published by the government and distributed to libraries, and especially to military officials, in all parts of the civilized world, some years later certain German officials discovered that this disease may be due to contact infection; and in announcing their results they made no mention of the work which had been done in the American Army. It may be of interest to add that, so far as we have information, typhoid fever was more prevalent in the German Army during the World War than in either the Italian, French, English, or American Armies.

Fly-Borne Typhoid.—Undoubtedly individuals had before that time suggested that the house-fly might be an agent in the dissemination of typhoid fever, but it remained for the Typhoid Commission of 1898 to bring this matter prominently before the people. They reported that in the first place they found that the disease was less frequent among those who ate in screened mess rooms than among those who took their food in unprotected quarters. Flies swarmed over infected fecal matter in the latrines and then visited and fed upon the food prepared for the soldiers in the mess tents. Lime was sprinkled over the contents of the latrines and within a few minutes, flies, with their feet whitened with lime, were seen walking over the food. It is possible for the fly to carry the typhoid bacillus in two ways. In the first place, fecal matter containing the typhoid bacillus may adhere to the fly and be mechanically transported. In the second place, it is possible that the bacillus may be carried in the digestive organs of the fly and deposited with its excrement on the food. Later, Hamilton, of Chicago, in a small epidemic confined to one ward of that city, caught flies in the vicinity of infected houses and demonstrated the presence of typhoid bacilli on or in these pests by cultural and agglutination tests. Thus the house-fly was incriminated and dubbed the "typhoid fly." Crusades against this pest have been waged, with more or less success, depending upon the intelligence and energy of the community. Now when intelligent people find flies in the dining-rooms of hotels, restaurants, and other places of refreshment, they turn away and seek more hygienic quarters in which to satisfy the demands of the body. The house-fly or the typhoid-fly, whichever we choose to call the beast, is an unmitigated pest and plays a part in the distribution not only of typhoid fever, but of other diseases; especially tuberculosis and dysentery.

The Incubation Period.—It is a matter of great epidemiologic importance to know as nearly as possible the period of incubation in this disease. In attempting to investigate this subject it is necessary to decide upon what point shall be taken as the basis of this determination. The Typhoid Commission of 1898 attempted in several ways to solve this problem. In the first instance, 40 nurses were sent from Chicago to the typhoid hospitals at Chickamauga and began attendance upon typhoid cases. The officers kept watch over these nurses and marked the day the first one showed symptoms of the disease. This proved to be ten days after arrival. The conclusion, therefore, was that from the time of the entrance of the bacillus into the body and the appearance of the first symptom of the disease is something less than ten days. It will be seen readily that there is a possible fallacy in reaching this conclusion. The commission had to assume that all the nurses reached the hospital uninfected and that the infection was acquired in the hospital, or at least after arrival at the hospital. Some of the regiments at Chickamauga arrived at the camp and the disease was widely disseminated among them when recruits were received. Note was made of the time when the first recruit placed in a typhoid area acquired this disease. This also proved to be about ten days. These findings have been confirmed by subsequent and more exact observations. About 50 accidental infections with the typhoid bacillus in which the exact time of the entrance of the bacillus into the body could be determined, have occurred. In one instance, an enthusiastic investigator decided to attempt to produce immunity by sterilizing and feeding typhoid cultures to some 20 volunteers. Within from six to ten days after a certain batch of cultures had been administered most of these men came down with typhoid fever. It was found from an examination of portions of the unused cultures that sterilization had not been complete. Other less striking and isolated instances of laboratory infection have occurred. In one instance an individual drank a culture of the typhoid bacillus with suicidal intent. The first symptoms appeared in eight days. It is worthy of note, and it may be added most fortunate to be able to note, that so far as we have information none of these cases has terminated fatally. However, they proved of the greatest value to science. There are but few diseases in which there has been opportunity to determine with so much accuracy the incubation period of acute infections in man. Now we know when the first case in an epidemic of typhoid fever occurs that the infection quite certainly happened from six to ten days before the first symptoms of the disease developed. A milk supply may scatter typhoid fever widely and still an examination of the milk supplied when the first case appears may on examination be entirely free from the bacillus. The same is true, of course, of water, food, or any other

agent by means of which the typhoid bacillus may find its way into the human body. These facts should always be held in mind when an attempt is made to trace an epidemic of this disease. As has been stated, four samples of water were examined at the height of the typhoid outbreak in Duluth, and only that taken from a tap which had not been turned for several days contained a suspicious organism.

It is a matter long ago observed and frequently recorded, that in armies an unusual number of soldiers show the initial symptoms of this disease after some not common exertion, such as a fatiguing march, participation in a battle, or some other exciting or exhausting exercise. For instance, in the Spanish-American War some of the regimental surgeons reported 50 or 60 new cases of typhoid fever the day after transfer from one camp to another. In some, this transfer covered only a few miles and was accomplished by a forced march. In others, it covered several hundred miles and consisted of a railroad journey. These reports are in part due to faulty records. Occupied with other matters concerned with the transfer, the medical officer does not return to his papers until he is located in his new home. Making due allowance for this and similar explanations which might be advanced, it seems highly probable that the development of the symptoms of such a disease as typhoid fever may be hastened by muscular exertion, which tends to force the bacilli from their resting places in certain tissues into the blood-stream. It is the destruction of the bacteria in the circulating blood in large numbers which constitutes the principal factor in causing elevation of temperature. On the other hand, there are cases in which the period of incubation, that is, the time from the entrance of the bacillus into the body until the development of the first symptoms of the disease, may be longer than ten days. This has been shown by a careful analysis of cases of laboratory infection. Sawyer, of California, has reported a local epidemic in which 93 people ate spaghetti which had been prepared by a typhoid carrier. Over half of these people showed symptoms of the disease before the eighth day. The earliest case developed on the third day. Quite naturally, we would expect considerable variation in the period of incubation in different individuals. During the incubation period the invading organism feeds upon the relatively simple proteins and possibly upon the amino acids of the body, and as a result of this feeding it multiplies. During the period of incubation in any acute infectious disease the invading organism supplies the ferments, the body of the host furnishes the substrate or food, body proteins and related substances are converted into bacterial proteins, the processes are synthetical and constructive, there is no poison set free, and no symptoms, recognizable at least, are developed. The period of incubation continues until the body cells become sensitized or

activated and pour out specific ferments which digest and destroy the invading organisms. In the active stage of an infectious disease the body cells furnish the ferments, the invading organism constitutes the substrate, the processes are destructive and analytical, complex proteins are broken into smaller bodies, poisons are set free, and the symptoms and lesions of the disease develop. With this understanding of the relation between the period of incubation and that of the active disease, it is only reasonable to suppose that there will be more or less marked variation in time before the body cells become sensitized and begin their destructive action on the invading organisms.

The Path of the Bacillus in the Body.—Practically in all instances, the typhoid bacillus enters the body through the mouth. In exceptional instances, theoretically at least, it is possible for it to be inhaled through the nose. However, in either case the bacillus is swallowed. The small amount of hydrochloric acid in the gastric juice has but little, if any, effect upon the growth of this organism. We have said that in all instances the bacillus is swallowed. This statement possibly should be modified to the extent of granting that it is possible that it may find its way into the blood through the tonsils. All the evidence we have suggests that there is at no time a marked multiplication of the bacillus anywhere in the alimentary canal. Even in the later stages of the disease when the feces may contain the bacillus in great numbers, it has been shown that the lower part of the intestine contains the bacillus in much smaller number than the upper portions. Cultures taken at different levels and in different parts of both the small and large intestine show that, while the duodenum may yield practically pure cultures, the numbers decrease and are overcrowded by other bacteria in the lower end of the small intestine and in the colon. So long as the typhoid bacillus remains wholly in the alimentary tract there is no development of the disease possible; in fact, as has been indicated, this specific bacillus is antagonized by the colon bacillus and by other inhabitants of the lower part of the small intestine and of the large intestine. It follows from what has been said that every one who swallows the typhoid bacillus does not necessarily develop the disease; in fact, there is really no infection until the bacillus passes through the walls of the alimentary canal and finds its way into the blood. As we shall see later, there are healthy carriers of this organism, some of whom have at some previous time suffered from the disease, while others have never developed symptoms.

From the fact that certain characteristic lesions, especially in Peyer's patches, are almost universally found in the intestines after death from typhoid fever, it was at one time assumed that these lesions mark the places where the typhoid bacilli penetrate the intestinal walls on their

way to the blood and to the lymph glands. Recent investigations have made it quite certain that this assumption is without warrant. The lesions found in the small intestine after death from typhoid fever are not due to the activities of the bacillus in finding its way through the walls, but are due to excretory poisons and may be induced, even in the lower animals, by the introduction of large numbers of dead bacilli into the circulation. Wherever they penetrate the walls of the alimentary canal on their way to the blood and lymph glands, whether it be through the tonsils or through the upper part of the small intestine, they leave no recognizable lesion. Having reached the blood the typhoid bacilli are in large part carried to the liver and discharged into the gall bladder. It may be remarked that this is the fate of many foreign proteins, be they living or dead, when introduced into the blood-current. Most unfortunately, human bile not only fails to destroy typhoid bacilli, but furnishes an optimum medium for their growth. Why the bile of man should favor the growth of the typhoid bacillus while it has a destructive action upon certain other pathogenic microorganisms, such as the pneumococcus and the tubercle bacillus, is an unsolved problem. It seems probable that if the bile had a marked bactericidal action upon the typhoid bacillus instead of furnishing a suitable medium for its multiplication, infection with this organism would be rare, and possibly man would be immune or possess a high degree of resistance to this disease. However, as it is, the bile of man furnishes an admirable culture medium for all the bacilli of the colon-typhoid group. It should be understood that the bacilli do not reach the gall bladder by ascension through the duct, but by descent from the circulating blood. This is true not only in man, but in some of the lower animals. It has been found experimentally that typhoid bacilli injected into the vein of a rabbit appear in the gall bladder as early as half an hour after injection into the vein. Multiplying in the bile, the gall bladder acting as an incubator, the bacilli are poured into the intestines where some of them again find their way through the walls into the blood. Thus a vicious circle is established and the gall bladder may continue to grow this organism and to pour it into the intestine long after the patient has recovered from the disease. In this way the typhoid carrier, to whom we shall refer in more detail later, comes into being and may contribute to the spread of the disease for months and even years.

Probably all pathogenic microorganisms have their predilection tissues in the body in which they tend to accumulate to cause histologic lesions and to reproduce themselves. So far as the typhoid bacillus is concerned such predilection places appear to be the bile, to which reference has already been made, the lymph nodes, the bone-marrow, the spleen, and the kidneys. They are also found in the rose spots, which

appear most abundantly over the abdomen and show during the second week of the disease. In the organs above mentioned, typhoid bacilli multiply and from time to time pass out and reach the general circulation. In these resting places they react with the normal tissue and cause cell proliferation. This occurs most markedly in the endothelial cells, and is in evidence in various tissues which furnish lodgment for the invading organism. The stimulus which leads to this cell proliferation is undoubtedly the poison formed by the death and disintegration of individuals of the invading hosts. Whether poisons formed by the typhoid bacillus are specific or consist of the protein poison formed by the disintegration of all proteins, is still a matter for discussion. Longcope has made a careful and valuable study of the changes in the bone marrow in typhoid fever. He has found that these changes consist essentially in hyperplasia of the lymphoid cells and endothelial phagocytes. These changes may extend and progress until necrosis of the tissue results. In this way the many complications that may occur in typhoid fever result. From time to time bacilli in smaller or larger numbers pass from one lymph node to another, from one organ to another, causing metastatic extensions of the disease. Experiments upon the lower animals have shown that typhoid bacilli may leave the circulating blood into which they had been injected and apparently find, at least temporary, safety in the lymph nodes, in the spleen, in the bone marrow, and possibly in other tissues as well. In these localities the bacillus not only escapes the greater danger of destruction to which it is subjected in the blood-current, but it finds itself so secure that it rapidly multiplies.

It is customary to attribute the lesions produced and found in typhoid fever to the specific toxin caused by this bacillus. The truth is that there is no sufficient evidence that the typhoid bacillus produces specific toxins. The word "toxin" now has a definite meaning. It is a substance which, when introduced into the animal body in repeated and increasing doses, stimulates the body cells to elaborate an antitoxin. Such are the toxins produced by the diphtheria and the tetanus bacillus; such are the toxins found in the venoms of serpents; such are the toxins found in certain vegetable proteins, as the castor bean and the jequirity. There is no evidence that the typhoid bacillus produces a substance which can be placed in the same group as the toxins just mentioned. As has been indicated, the typhoid bacillus finds its way through the walls of the intestine without leaving any recognizable lesion. Instead of undergoing destruction or suffering diminution in numbers in the gall bladder, as many pathogenic organisms do, it finds in the bile a suitable medium for its growth and multiplication. Increased in numbers in the bile, it is again poured into the intestine, it again pierces the

intestinal walls, and it is carried by the blood, and possibly by the lymph, to the lymph nodes, such as the mesenteric glands, to the spleen, to the bone marrow and other tissues, in which it finds not only a safe resting place, but incubators in which it multiplies. The lesions of typhoid fever are not the results of specific toxins, because there is no evidence that this bacillus produces such bodies, but result from the action on the body cells of the protein poison set free in the destruction of the invading organism by ferments elaborated by the sensitized body cells. The old view that the symptoms and lesions of typhoid fever result directly from the activity of the living bacillus is not justified by the most recent scientific work. During the period of incubation in this disease the bacillus is multiplied in the bile, in the lymph nodes, in the spleen, in the bone marrow, and possibly elsewhere in the body, and still at this time there are no symptoms and no lesions. There is no fever, for instance, until the body cells, having been sensitized, pour out ferments which split up the typhoid protein and liberate the protein poison. It is still a matter for future investigation to determine whether the protein poison resulting from the cleavage of the typhoid bacillus is any different in its chemical composition or in its toxicogenic action from that obtained from other microorganisms. There are differences probably in chemical structure and corresponding differences in action between the protein poisons furnished by the cleavage of different proteins, whether they are bacterial or non-bacterial. Fevers with many of the characteristics of typhoid fever have been induced in the lower animals by repeated injections of such proteins as egg white, the casein of milk, the edestin from hemp-seed, etc.

It is essential to a thorough understanding of the epidemiology of this disease to make some statements concerning its complications and its sequelae. There are but few, if any, diseases more liable to complications and to relapses than typhoid fever. Whipple states that complications are responsible for two-thirds of the deaths that occur in this disease. In the first place, relapses are frequent. The fever has disappeared, the patient is apparently on the high road to complete recovery, when suddenly, after a few days or even after a longer time, typhoid fever begins all over again. This is due probably to the fact that the bacilli which have passed from the general circulation into the predilection organs already referred to, are again poured into the blood. In the gall bladder they not only find the bile a suitable medium in which they can multiply, but they attack the walls of the gall bladder, setting up a cholecystitis, which may persist for years and possibly furnish the base for the formation of gall stones. Intestinal hemorrhage occurs in a considerable percentage of cases and is sometimes suf-

ficiently great to cause death. Intestinal perforations may occur and necessitate immediate surgical interference or terminate fatally. The typhoid bacilli accumulate in the lungs and either directly induce pneumonia or prepare the ground for the invasion of pneumococci or other pneumonia producing organisms. Typhoid-pneumonia is not an infrequent occurrence in terminal typhoid fever. Necrotic changes may occur in the kidney, liver, larynx, and other parts of the body. Collections of typhoid bacilli may lead to abscesses which discharge virulent organisms, sometimes for years after the individual has recovered from the disease. The chronically infected gall bladder or a typhoid abscess makes individuals thus afflicted sources of continued danger to others. It is, therefore, essential that the epidemiologist in investigating outbreaks of typhoid fever have all these things in mind.

Whether any lower animals naturally have typhoid fever or closely related diseases is a matter about which we have no exact information. As long ago as 1883, Sutton reported a disease closely resembling, in fact he regarded it as identical with, typhoid fever, in some monkeys. In one of these, autopsy showed ulcerations quite typical of typhoid fever in man, accompanied by perforation. Indeed, as early as 1823, Magendie induced intestinal lesions similar to those of typhoid fever by the intravenous injection of putrid substance. Of course, now, no one would claim that this condition is comparable with typhoid fever. It does emphasize, however, a matter of importance; and that is, that the intestinal lesions in typhoid fever result from the excretion of poisonous substance and are not due to the action of the living bacilli in attempting to penetrate the intestinal walls. Hundreds of experiments have been made upon laboratory animals in attempts to induce typhoid fever. On the whole, it can be said that no one has been successful. Partial success has resulted, especially when mixed cultures have been used or when some other organism in sterilized culture has been simultaneously introduced into the animal. Sanarelli injected sterilized cultures of the colon bacillus intraperitoneally and simultaneously injected the typhoid bacillus subcutaneously. In this way he produced intestinal lesions resembling those of typhoid fever.

As long ago as 1888, Vaughan injected into the abdominal cavities of three dogs a typhoid-like bacillus obtained from a drinking water which had caused a severe epidemic. These animals were kept with a control. The three inoculated animals showed a fever quite characteristic of typhoid, which ran at its height from 105° to 106.8° . Two of these animals died and both showed lesions similar to those found in man after death from typhoid fever. The culture used in this experiment was not that of a typical Eberthian bacillus, and for this reason at that time even the author did not claim that he had induced typhoid

fever in these animals. It may be said that the control kept along with the infected ones showed no abnormality.

In 1911, Metchnikoff and Besredka, repeating experiments which had already been made by Grunbaum, failed to induce any fever in chimpanzees by feeding them with pure cultures of the typhoid bacillus, but on feeding these animals with typhoid stools they did succeed in inducing symptoms and lesions so characteristic of typhoid fever that their work is today accepted as proof that typhoid fever may be induced in chimpanzees. Moreover, they obtained cultures from the animals in which the disease had been induced by feeding with typhoid stools, and these pure cultures caused the disease in other chimpanzees.

While the production of unquestionable typhoid fever in laboratory animals has not been an unqualified success, it has given us much information concerning the path of the bacillus through the body. So many cases of accidental typhoid fever have been reported in man that, even if all experiments on the lower animals, including those on chimpanzees, be discarded, every condition essential to proving that the typhoid bacillus is the cause of the disease in man has been complied with. There can be no question about this.

Typhoid Carriers.—By this term we designate those individuals who are eliminating typhoid bacilli at times when they themselves are apparently well. Typhoid bacilli may appear in the feces, and even in the urine, after they have gained entrance into the body and before they have induced symptoms of the disease. More frequently, these bacilli continue in the feces and urine during convalescence and after complete recovery. As we have seen, typhoid bacilli occur abundantly in the gall bladder, from which they are constantly being passed into the bowels. Sometimes, after recovery from typhoid fever, discharging abscesses, which are formed during the course of the disease, continue to eliminate these microorganisms. They have been found in rectal abscesses after typhoid fever and have been known to continue in the discharges from these for many years. Rarely, one who has never had typhoid fever becomes a carrier and is a source of danger to those with whom he associates. Typhoid carriers may be temporary or permanent. The history of Mary Mallon, who, under the name of "Typhoid Mary," was investigated with great perseverance and skill by Soper, now stands out as a prominent figure in the epidemiology of this disease. In the winter of 1906, Soper was called upon to investigate a household epidemic which had broken out in a country place at Oyster Bay in the latter part of the preceding August. Six persons in a household of eleven had had the disease. The house was large, surrounded by ample grounds, and was occupied during the summer by a wealthy banker from New York. The first case appeared on August 27 and the last on

September 3. Typhoid fever was an unusual disease in the neighborhood and at the time of the outbreak no other case was known and none followed. The water, milk supply, cream, and other articles of food, had been eliminated as possible causes. From a sanitary standpoint everything about the place was in most perfect condition. At one time it was suspected that soft clams, which had been obtained from an Indian woman, had caused the epidemic, but other people had eaten these clams; and, moreover, they had not been eaten in the family for six weeks before the outbreak of typhoid. There had never been any typhoid fever in the house, nor had it been visited by a convalescent from this disease. The members of the family who were taken ill had not been away from Oyster Bay during the period of incubation. The first member of the family to come down with the disease was a daughter, the next two were maid-servants, then came the wife, another daughter, and finally the gardener, who resided permanently at Oyster Bay and had lived on the place for many years. Soper found on inquiry that the family had changed cooks on August 4, about three weeks before the appearance of the epidemic. The new cook remained in the family about three weeks after the outbreak of the disease and her present whereabouts were unknown. Soper started out to find this temporary cook and in his search he was aided materially by the head of the employment bureau where she had been recommended. At last Mary Mallon was found and her previous history traced. It was shown that during the preceding ten years she had worked in eight families, in seven of which typhoid had occurred. When found, Mary was unwilling to aid in incriminating herself and refused to give her history or to answer leading questions. It became necessary for the Board of Health of the city of New York to arrest her and place her in a detention hospital, where thorough studies of the urine and feces were made. No bacilli were found in the former, but the latter contained them in great number. Daily examinations made over two weeks failed only twice to reveal the presence of the bacillus typhosus, and on these occasions the sample taken was perhaps too small. From March 20 to November 16, 1907, the stools were examined three times a week, and in only a comparatively few instances did these examinations fail to reveal the presence of the bacilli. Soper states:

"The implication was plain. The cook was virtually a living culture tube in which the germs of typhoid multiplied and from which they escaped in the movements from her bowels. When at toilet her hands became soiled, perhaps unconsciously and invisibly so. When she prepared a meal, the germs were washed and rubbed from her fingers into the food. No housekeeper ever gave me to understand that Mary was a particularly clean cook."

Mary Mallon was kept in detention by the Department of Health for three years. She was allowed to receive friends and enjoy such

privileges as were possible, but never became reconciled to her detention. Legal attempts were made to secure her release, but the courts held that the Department of Health acted within its rights in keeping her in custody and that in doing so public interests were being served. In 1910, on her promise not to take employment as a cook or engage in an occupation which would bring her into contact with food, she was discharged. She broke her parole and disappeared. Her whereabouts were not known for nearly five years. In January and February, 1915, an outbreak of typhoid occurred in the Sloane Hospital for women in New York City. There were 25 cases, mostly among the nurses and other attendants at the institution. This hospital is one of the most capably managed institutions of its kind and is noted for its cleanliness. An investigation showed that Mary Mallon, under the name of Mrs. Brown, was the cook. She was arrested and placed in a detention hospital where she remains at the present time (1922).

Soper states:

“The total number of outbreaks of which Typhoid Mary is known to be the cause is ten; the total number of cases fifty-one. Owing to the fact that only parts of her entire history are known, it is probable that the total number of outbreaks for which she is responsible is much larger than this record indicates. It would surprise nobody to learn that she had produced some extensive epidemics. * * * * The story of Typhoid Mary indicates how difficult it is to teach infected people to guard against infecting others. Mary had ample opportunity to know the danger which she constituted toward those whose food she prepared. She knew from being told and she knew by experience. She was aware of the penalty which she would suffer if she broke her parole and caused another outbreak. That she could have avoided spreading infection by obeying her instructions admits of no doubt. She knew that when she cooked she killed people, and yet she deliberately sought employment as a cook in a hospital. Why did she do this?”

It is impossible at the present time to make any estimate of the number of typhoid carriers in the country at large or in any given community. The New Jersey State Department of Health in its 1920 report mentions 14 known chronic typhoid carriers which they discovered during a period of eight years. To each of these individuals one or more outbreaks of disease were traced. One man in particular is known to have been responsible for three distinct outbreaks in which there were 73 cases and 3 deaths. The man was a dairy worker, and in spite of knowledge of his own condition and of warnings of the danger he constituted, he persistently stuck to his original occupation. The existence of such persons must be borne in mind in all epidemiologic studies and in attempts to control the disease. These facts are recognized quite generally by health authorities and in most cities the examination of all handlers of foods in hotels and in restaurants is required. In the army camps during the war all food handlers were

examined, and it is gratifying to state that but few carriers were found. Seven chronic carriers were sent to Walter Reed Hospital, where extirpation of the gall bladder was resorted to. In five of these, the individuals ceased to discharge typhoid bacilli.

The persistence of typhoid bacilli in the body after recovery from the disease seems to have but little, if any, effect upon the individual. Typhoid carriers may be and may remain in perfect health while they are continually eliminating the microorganism and possibly infecting others. In these people urinary carriers are rare, while those whose intestinal discharges are infected are relatively large. In rare instances the urine may be turbid with bacilli and each c.c. may contain many billions. During the second or third week of the disease the bacillus is found in from one-fourth to one-half the cases in the urine. Rarely, typhoid bacilli cause cystitis and this chronic condition may continue quite indefinitely, and of course is accompanied by the constant discharge of typhoid bacilli. A few cases of urinary carriers have been reported in which there was no history of previous typhoid fever. As a rule the nidus for the growth of these bacilli, so far as the urinary organs are concerned, is in the pelvis of the kidney rather than in the bladder. Out of 314 carriers Prigge found only 23 who were pure urinary carriers. Gay states:

"It is evident (from figures given in a table) that continued excretion of the typhoid bacillus, largely through the feces may be anticipated in four or five per cent of all recovered cases. There is no reason to assume that once the chronic carrier state has been established, at a period arbitrarily placed at three months after recovery, the excretion of bacteria becomes progressively less with succeeding months and years; in fact, all evidence points to the contrary. These percentages are certainly under the true percentages, owing not only to the difficulty in isolating the typhoid bacilli from the feces of relatively normal individuals even when cathartics are employed, but owing to the fact that the discharge of the microorganisms in carriers is characteristically intermittent. Thus, the high percentage of 11.6 reported from the Central Research Institute at Karauli in India by Semple and Greig more nearly represents the true state of affairs, as the search for bacilli was made daily until the stools were repeatedly negative. But, if we assume as a minimum that five per cent of all recovered cases become chronic carriers and we know that over 150,000 recovered typhoid cases are still being produced each year in the United States, we have some 7,500 carriers added annually to a presumably cumulative list. It is evident how important any measures directed towards the detection and cure of these fundamental sources of further typhoid infection become."

Gay, who has diligently collected and carefully investigated the data concerning typhoid carriers, estimates that there are at least three such carriers in every 1,000 of the population at large, and he considers it conservative to attribute from twenty-five to thirty per cent of all cases of typhoid fever to carriers. Garbat is less conservative and thinks that fifty-five per cent of all cases of typhoid fever may be traced, directly

or indirectly, to carriers. With all the precautions now taken in the treatment of this disease, it is not the man who is sick in bed with typhoid who is a source of danger to the community so much as is the man who is supposed to be well, mingles with others, and eliminates from his bowels or kidneys or from both, typhoid bacilli. This condition renders the absolute eradication of this disease a very difficult problem. It is impossible to examine the excretions of everybody for typhoid bacilli, and besides, were such a Herculean task undertaken the fact that the elimination of these microorganisms is intermittent would lead to failure to detect many carriers. The best we can do is to cause the thorough examination of the excretions of all who are engaged in the handling of food. Moreover, such examinations must be repeated from time to time. Usually the cooking of food necessitates a temperature high enough to destroy typhoid bacilli, but this is not always true and great danger lies in those foods which are not cooked and the handling of all food after cooking. The more closely people are associated the more dangerous becomes the carrier of typhoid bacilli and other pathogenic organisms.

While, as has been stated, Budd and other early writers reported that those who had recovered from this disease may still transmit it to others, the first actual demonstration of typhoid bacilli in the stools of those free from typhoid was made by Remlinger and Schneider of the French Army Medical school at Val de Grace in 1897. The first German work on typhoid carriers was not until five years later (1902).

Air-Borne Typhoid.—Is typhoid fever ever disseminated through the air? This is a question to which diverse answers have been given. Our present knowledge of the etiology of this disease gives no support to the old belief that it may be caused by the inhalation of gases from decomposing organic matter. Infection can result only from specific bacilli and no amount of decomposing matter in which this organism is not present can cause the disease. Moreover, the specific cause of typhoid fever is a particulate body and not a gas. Inhalation of gases from putrid material may cause intoxication but not infection. Cases reported by older writers in which typhoid fever was believed to be due to the inhalation of gases from putrid material were, as we can now see, not instances of infection. In illustration, we shall mention the Clapham epidemic as reported by Murchison. Twenty out of twenty-two school boys who watched the opening of a pit that contained a large amount of decomposing organic matter and which had been closed for some years were within three hours prostrated with vomiting and diarrhea. Two died, one within 23 and the other within 25 hours. Examination showed an acute swelling of Peyer's patches and the solitary follicles, with slight ulceration of these structures, together with con-

gestion of the mesenteric glands. These were diagnosed as typhoid fever, but we now know that they were instances of acute poisoning with noxious gases. The typhoid bacillus is generally destroyed by other bacteria or their products in material sufficiently advanced in putrefaction to give off unpleasant odors. The oldest cultures of this bacillus are free from disagreeable smells, and infection with typhoid fever is not likely to result from ingestion of putrid matter. Unfortunately, there is nothing about food or drink infected with this bacillus to indicate to the unaided senses the presence of such infection. Water containing typhoid bacilli may be clear, sparkling, and agreeable to the taste. Milk infection with this microorganism reveals no peculiarities to taste, sight, or smell. A fly may deposit typhoid bacilli upon a cooked potato without rendering this article less palatable to the consumer. We wish to emphasize the difference between the question now before us as to whether typhoid fever may be disseminated by infected particles of dust carried through the air, and the older idea that it was spread by the agency of gases given off from putrid material. We may state as a bacteriologic fact that gases given off from putrid organic matter contain no bacteria. Certainly, this is generally true, and we know of no exception. On the other hand, a wind may carry partially dried infected particles of dust which may be deposited on food or inhaled and cause typhoid fever.

Germano has collected the literature bearing upon this question and has added his own experimental data. The following report by Chour, a Russian medical officer, is given as an instance of air-borne typhoid fever. A typhoid epidemic appeared in two infantry regiments. All the soldiers of these regiments obtained their drinking water from the same source. One regiment had in 1885, 9.6 and in 1886, 3.2 per 1,000 cases of typhoid fever. The second regiment had during the same time a similar proportion of cases, but in one company of the Second Regiment 14 out of 90 men were stricken with the disease. The extraordinary number of cases of this disease in this company led to the supposition that the part of the garrison occupied by these men was specifically infected. In December, 1886, the room occupied by this company was vacated and subjected to thorough disinfection. The walls, the floor, and the furniture of the room, also the clothing of the soldiers, were disinfected. After this had been done the company was allowed to return to its own quarters. In 1887 the number of cases of typhoid fever in this company was reduced to 1.7 per 1,000, and in 1888 there was not a case, while during the same time typhoid fever increased among the soldiers occupying the parts of the garrison which had not been disinfected. The disappearance of the disease among the soldiers who occupied the disinfected quarters and its persistence and increase among those in the undisin-

fecting quarters led Chour to conclude that the typhoid bacillus was disseminated through the dust in the rooms. It is more than likely that the bedding and clothing of these soldiers were soiled with typhoid stools and the bacilli were transferred from these soiled articles to the alimentary canals by means of the fingers; in other words, these were cases of contact infection.

The second citation by Germano is a report by Favier. On August 26, 1886, a regiment of dragoons in which there had been no typhoid fever, left Compiègne for the annual maneuvers. From the above mentioned date until September 6 of the same year, one half of this regiment was quartered at the village of Cuvilly, while the other half was divided between Neuville and Ressous. On the last mentioned date the troops reunited at Compiègne. On September 11 a dragoon who had been quartered at Cuvilly was taken with typhoid fever. From this time to October 2 of the same year, eight other cases appeared in this half of the regiment, while only two cases appeared in the other half, and the first of these had its initial date October 5. Investigation showed that during the stay of the troops at Cuvilly there were three cases of typhoid fever in a family at that place. The soldier who first contracted the disease had been quartered in this house and the next two cases to develop the disease were men who had visited the house. Favier thinks that the man quartered in the infected house at Cuvilly received the infection through the air inhaled at that place and that the soldiers visiting this house were infected in the same way; also that the disease spread to the half of the regiment which had not been at Cuvilly through the air. In the light of today, this conclusion is by no means warranted. The soldier quartered at the house of the sick may have been infected by personal contact, through his drinking water, or through his food. These possible methods of infection are also applicable to the men who visited this house. These men may have carried the infection in their clothing or on their persons to their comrades. When the halves of the regiment were united in the common barracks at Compiègne, common drinking cups may have become infected and may account for the spread of the disease. We are inclined to reject this report as evidence that typhoid fever may be disseminated through the air.

The third citation is from Olliver, who states that a girl sick with typhoid fever was placed in a hospital ward in which there were no other cases of this disease. Soon thereafter two other patients in the same ward developed typhoid fever. One of these occupied the bed by the side of the first patient and the other a bed opposite. The ward was vacated and thoroughly disinfected, after which there was no typhoid fever. The disinfection of the ward was justified, but the con-

clusion that the disease was spread through the air is by no means warranted. It is more than probable that attendants carried the bacteria on soiled fingers from one patient to the other, or that common drinking cups were used. The history of these cases teaches, as many similar instances indicate, that it is not safe to place typhoid fever patients in a ward occupied by those suffering from other diseases; or, in other words, it teaches the desirability of the isolation of typhoid cases and greater care among common attendants, but it furnishes no proof that typhoid fever may be disseminated through the air.

The corpse of a woman who had died from typhoid fever at Rheims was brought to Vassognes for burial. The body had not been embalmed. It was transported in a wooden coffin, and at the time of burial was in an advanced stage of decomposition. A few days later three children of the dead woman came to Vassognes. These soon sickened with typhoid fever and the disease spread until it had infected many persons in the village. The reporter of these cases concludes that the bacteria were disseminated through the air. Soiled hands and clothing were more likely factors in the spread of the infection.

In July, 1886, a woman from Paris came to a hotel in the village of Eaux Bonnes, where she soon developed typhoid fever. A short time after, three daughters of the proprietor of the hotel were taken sick with the same disease. Beyond these cases the epidemic did not spread. This undoubtedly is another instance of contact infection. It may have been that those attending the sick woman handled the food of the children without disinfecting their hands.

The military station at St. Bernard lies about four kilometers south of Antwerp and 1,800 meters from the point where the Rupel flows into the Schelde. Usually four regiments of infantry were located at this place. For three years there had not been a case of typhoid fever among the soldiers in these barracks, when in August, 1892, a severe epidemic appeared. The water-supply was not changed nor were the barracks disinfected. The first case appeared August 22 and the last October 20. The explanation given by Froidboise is as follows: On account of some engineering work which was being done in the Schelde at the mouth of the Rupel the latter stream overflowed its left bank and distributed a large amount of sewage brought down from Brussels and Mechlin. The receding water left a thin deposit scattered over several thousand acres of land. As this deposit consisted of sewage it is more than likely that it contained typhoid bacilli in large numbers. From August 12 to October 10, the direction of the prevailing wind was such that it would carry the dust from the drying deposit into the garrison. Before and after the dates mentioned above, the wind was in the opposite direction. The question is whether or not the typhoid bacillus

can be carried in particles of dust suspended in the air through a distance of 1,800 meters. Germano concludes that this is impossible, and we agree that it is quite improbable. It is more likely that the infected dirt was carried on the feet of some one.

A man while away from home contracted typhoid fever and returned to his native village, in which there had not been a case of this disease for a long while. The undisinfected feces from this man were thrown upon a dung heap. Some weeks later five men carted away this material, and later four of these developed typhoid fever and the fifth suffered from intestinal catarrh accompanied by enlargement of the spleen. The undisinfected dejections from these men were thrown upon another dung heap. A few months later two men removed this material and one of these developed typhoid fever. Brouardel supposes that the typhoid bacilli were disseminated through the air from the decomposing dung heaps. Germano thinks it more probable that the men engaged in this work soiled their hands and in this way transferred the bacilli to their mouths. This is more probable.

After reviewing the literature as stated above, Germano endeavored to decide the question concerning the possibility of dissemination of typhoid bacilli through the air experimentally. He found that typhoid bacilli mixed with dust from different sources and thoroughly desiccated speedily die, and he concludes that air infection, through many hundred meters at least, is impossible. More recently, Neisser has shown that dust infected with the typhoid bacillus may be carried by a current of air moving at a rate of 1.7 centimeters per second through a distance of 680 centimeters and there deposited with the germ still possessed of vitality. He concludes that since this bacillus is not transported to a distance of more than 680 centimeters by the air moving at a rate which generally prevails within a room, that typhoid fever cannot be considered a dust-borne disease. This conclusion has reference only to the possibility of the typhoid bacillus floating through the air of a closed room; but even within doors the air often moves with a velocity many times greater than 1.7 centimeters per second. Especially is this true when the movement of the air within the room is influenced by drafts from windows, doors, and ventilating flues. Partially dried typhoid stools on the floor may be sufficiently comminuted to form a dust which may float through the air, be deposited on food, find its way into uncovered receptacles of water or milk or be directly inhaled, find lodgment in the nose and pharynx and finally reach the intestines.

The danger of air infection with typhoid fever is greatly increased in military life, where food and drink are often exposed for hours to an atmosphere laden with dust and possibly infected with the typhoid bacillus. The shell roads through the encampments at Jacksonville,

Fla., during the Spanish-American War were ground by the heavy army wagons into an impalpable dust several inches thick. Along these roads scavengers carted in half barrels fecal matter containing the typhoid bacillus. The contents of these tubs frequently splashed and overflowed in this dust. On each side of these roads soldiers were encamped and many mess tables were in close proximity to the roads. Local whirlwinds sometimes caught up large quantities of this dust and carried it long distances. After seeing these things, we feel that we cannot exclude the dust as a probable carrier of typhoid infection, notwithstanding the fact that it would be a difficult thing to scientifically demonstrate that the disease has been disseminated in this way.

Seasonal Prevalence of Typhoid Fever.—Since recognized as a distinct entity, it has been observed that typhoid fever is most prevalent in the summer and fall; indeed, so marked is this that it has often been designated as “estivo-autumnal fever.”

The proportional distribution of typhoid deaths by months is graphically shown for certain divisions of the U. S. Registration Area for the five year period 1911-1915. For the area as a whole the peak occurs in September. This is true for the cities in registration and nonregistration states. In the rural sections the peak is in October. March, April and May are months of lowest incidence. In the nonregistration cities, mostly southern, typhoid begins its ascent in June, a month earlier than the other groups. Its descent is likewise about a month ahead of the others. In this connection it may be noted that the seasonal distribution of typhoid in U. S. Registration Cities has altered in the twenty years since 1900. Thus, for every 100 deaths in September, 1901 to 1904, there were 69 in January. In the period 1916 to 1919, for every 100 deaths in September there are only 41 in January. This same shifting is seen in the rural part of registration states. Thus in the early period, for every 100 deaths in September there were 60 in January, while in the later period, for every 100 in September there were only 30 in January. One interpretation of this change is that by the improvement of water-supplies the all-year-round typhoid due to water has been diminished, whereas the autumn typhoid due to bathing, flies, infected food and contact has not been affected by this improvement. Thus the disparity between autumn and winter typhoid is greater now than formerly. It is more difficult to explain the rural change, for supposedly improvement in small water-supplies and individual well supplies would not be expected to show the mass improvement realized in the cities. On the other hand, this apparent reflection in water-supply improvement may be the result of a change in the composition of the registration area. Thus in 1904 the registration area and cities in nonregistration states were represented in greatest numbers

by the northeastern section of the country. Since that time the southern and western territory has been added. The population of the registration cities grew from 23,000,000 to 37,000,000 in the period under consideration, and the population of the rural part of the registration states increased from 9,000,000 to 35,000,000. Some would attribute the greater prevalence of the disease during the autumn to the warmer temperature. We do not believe that this is the true explanation. In the summer and fall there is more marked pollution of the soil and greater

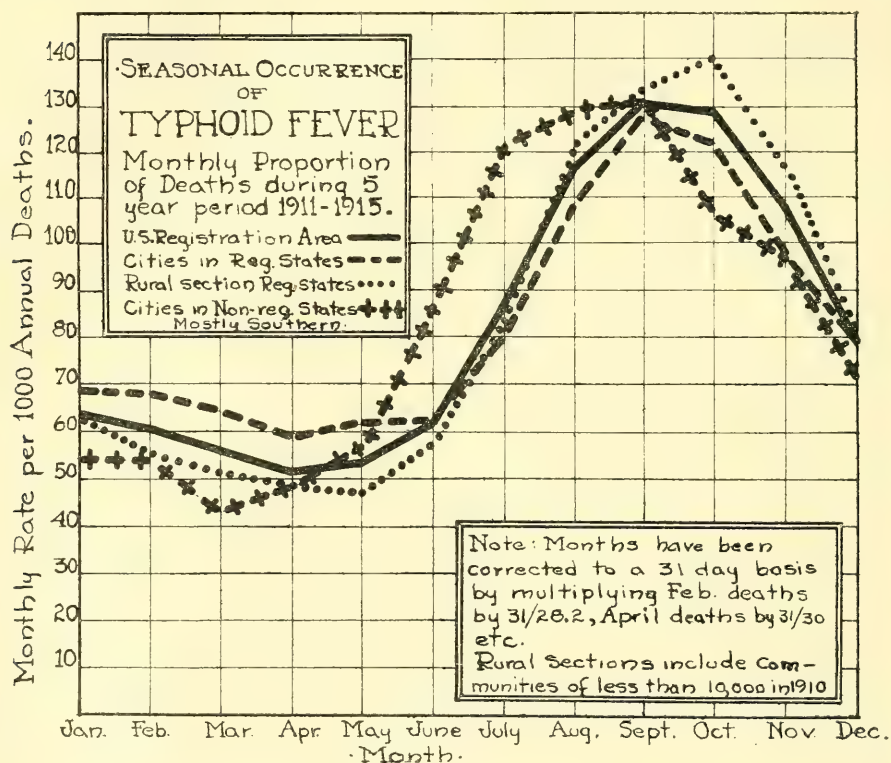
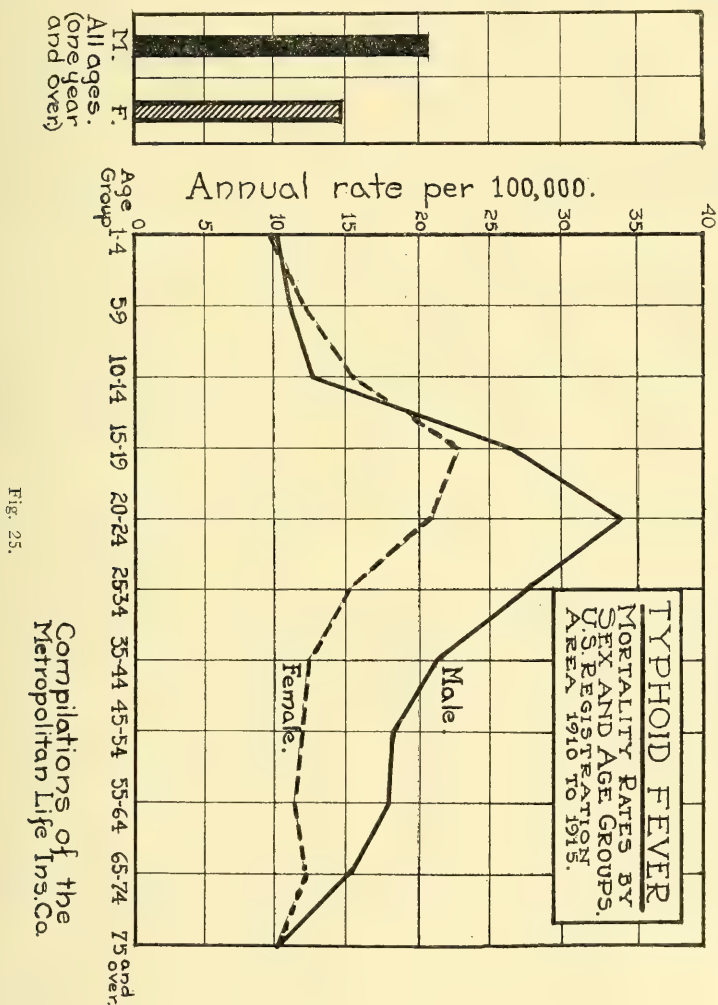


Fig. 24.

opportunity for the contamination of food and drink, as well as soiling of the person and clothing with infected material. During the warm months careless persons scatter excreta quite indiscriminately over the land. In the colder seasons they are more likely to resort to special places for the deposit of excrement. Flies abound during the warm months, feed upon excreta deposited on the surface and in pits, and then visit dining-rooms, mess halls, etc. Frequent rains during the summer and fall wash infected material deposited on the soil into the water-supplies. Fruits and vegetables lie on the ground and often come into contact

with human manure, which may be specifically infected. During the warm months pedestrians tramp through the woods and bushes where excrement has been deposited and are liable to carry infected material into their homes. Heavy rains may within a few hours wash tons of excrement scattered over square miles of territory into the reservoir of



some city water-supply. In the winter there are no such opportunities for the wide dissemination of infected fecal matter. When deposited out-of-doors it is soon frozen, is not scattered, and is likely to be held in the place of deposit until the specific bacilli which it contains are destroyed. Many local epidemics of typhoid fever have been traced to the melting of snows upon which typhoid stools had been deposited.

This is true of the notable epidemic at Plymouth, Pa., some years ago. The dejections from a typhoid patient sick in a house near the head of the water-supply were thrown in an undisinfected condition on the snow. When the snow melted the infected material was carried directly into the water-supply and caused, in proportion to the number of inhabitants of the place, one of the most serious epidemics of this disease known in the annals of epidemiology.

It is worthy of remark at this place that typhoid fever is much more prevalent among men than among women, among young adults than in either childhood or old age. Some would attribute these facts to differences in sex and age. We are inclined to believe that sex *per se* has nothing to do with it and age comparatively little. Man is more likely to be infected than woman because of his wider range of activity and his greatly increased chance of exposure to infection. The young adult male has the widest range of activity, is more careless than his more experienced elder brother, and multiplies his chance of infection by his wanderings and his carelessness. The wife is at home, drinks a safe water, does not mingle with typhoid carriers, and is not likely to soil her person and clothing with specifically infected material. The husband goes up and down the country, drinking water from questionable sources, eating food prepared by diverse and for the most part uncleanly people, and mingles more or less intimately with all kinds and conditions of men among whom there may be typhoid carriers.

Typhoid Fever in Armies.—In past centuries typhoid fever was one of the most potent causes of sickness and death in armies. This was due to many factors. In the first place, the average age of the soldier covers that period in life in which man is most exposed to this disease. This, together with the necessity of drinking contaminated water and the crowding which is essential to military life, often made typhoid fever a greater factor in the death rate than the missiles of the enemy. Conditions were most favorable for the development of water-borne and contact typhoid. In briefly reviewing the history of typhoid fever in armies, we shall not select instances where the death rate from this disease was most appalling, nor shall we go back far into history, before this was recognized as a distinct disease; but shall content ourselves with a few historical illustrations, choosing especially those instances which, in the light of today, most illuminate the epidemiology of the disease. In our own Civil War we knew nothing of the specific cause of this disease, and thus there is very little of value along this line in the splendid volumes which contain the medical and surgical history of the War of the Rebellion. In these records there is but little information concerning the importation of typhoid fever, more attention being given to general reports concerning hard service, inclemency of

the weather, and insanitary conditions in camp as connected with the prevalence of this disease. More importance is attached to exposures, hardships, the unaccustomed mode of life of the young soldier, overcrowding and bad ventilation, than to importation of the disease from the localities from which the men were recruited, although this is occasionally suggested. The absence of satisfactory reports on the causation of typhoid fever in the camps is attributable to the difficulties attending investigation into the origin and transmission of this disease, the causative factor of which at that time was unknown. It is estimated that during the Civil War there were in the Union Army 75,361 cases of this disease with 27,056 deaths. These figures do not include many cases which we now know were typhoid fever but at that time were reported as typho-malaria and under various other names now fallen into disuse.

When the Franco-German War began, every corps of the German Army was infected with typhoid fever and the Second Division of the Eleventh Corps was having at that time a marked epidemic of this disease. The infection was not confined to the Prussians but extended to every contingent of the German Army. The seeds of the disease carried with them, rapidly bore fruit, especially among the troops besieging Metz and later among those besieging Paris. Within less than two months after war was proclaimed typhoid fever had extended so widely among certain divisions of the German troops, notably in the Eleventh Corps of the Prussian Army and in the Württemberg Division, that more than fifteen per cent of the men of these commands were sick with this disease. The total number of cases among commanding officers and men in the German Army during the Franco-German War amounted to 73,396, which is equivalent to 9.31 per cent of the average strength of the army. It will be remembered that the invasion of France began about the middle of July, 1870. During the second half of this month the total number of cases of typhoid in the German Army was 345, less than the average for preceding years of peace. In August, the number increased perceptibly and amounted to 2.6 per 1,000, but this was not sufficient to cause alarm, and up to the beginning of September it could not be said that there was an unusual prevalence of this disease. However, early in this month there was an explosive outbreak and the cases ran up to 12,463, equivalent to 15.3 per 1,000. October saw 17,253 new cases. In this month the epidemic reached its climax, and fell slowly until January, 1871, and more rapidly to June, but at the last mentioned date it had not reached the peace level. During the fall of 1870 there was not a regiment in the German Army free from typhoid fever. In addition to the importation of typhoid fever, the Germans invaded a country in which this disease was then and

still remains endemic. However, the point which we wish to emphasize here is that the invading army transported typhoid fever with it and that from seeds thus carried the disease spread until no regiment remained free from it. There were in the German Army during this war 8,786 deaths from typhoid fever, making sixty per cent of the total mortality during this period.

In the minor wars waged by the British Empire, it has been demonstrated repeatedly that typhoid fever may be transported along with an army into regions where man has never previously lived. This was illustrated in the Afghan War from 1878 to 1880. Several of the encampments of the English soldiers during this invasion of Afghanistan occupied positions probably never before occupied by human beings. It is not at all likely that the water which was obtained from mountain streams in the invaded region was specifically contaminated with the bacillus of typhoid fever; nor was it likely that the virgin soil covered by these encampments was infected, except as it became so by occupation, and yet typhoid fever occurred at nearly every station occupied by the English troops. Only one explanation of the prevalence of this disease in these places is possible. It is known that the English troops which had been encamped in various parts of India were widely infected with typhoid fever when the invasion of Afghanistan was begun.

Similar experience is furnished by the history of a French expedition in northern Africa. In the Oran campaign in 1885 French commands encamped in desert stations never before occupied and in these typhoid fever not only appeared, but acquired epidemic proportions. At the time of the Suakin Expedition in 1885 it was believed that typhoid fever is always a water-borne disease, and consequently every precaution was taken to insure a pure water-supply for the troops; in fact, all the drinking water was distilled. Notwithstanding this, typhoid fever prevailed extensively. At least one regiment, the East Surrey, joined the expedition already infected with typhoid fever. It is more than likely that these men infected the latrines and that flies aided in the distribution of the disease. Moreover, it is quite certain that contact infection, then unknown, played an important part in the continuance and spread of this disease.

In the expedition for the relief of Chitral, from March 28 to August 24, 1895, typhoid fever was carried with them by the English soldiers. The first recognized case of this disease occurred April 29, although this had been preceded by several other cases the diagnosis of which had been doubtful at the time and which had been transferred to base hospitals, proving later to be typhoid fever. The expedition consisted of two regiments, with a total strength of 1,601 officers and men. After battles at Malakand and Kahr, April 3 and 4, these regiments were en-

camped at Kahr, in the Swat Valley, 2,000 feet above sea level. The health was good at first, but with the increasing heat the men, who were much crowded in small single fly-tents, began to suffer from malarial fever and typhoid soon made its appearance. From April 29 to August 4, the time of the arrival of the expedition at Laram Kotal, 172 cases with 39 deaths, were reported. In regard to this epidemic, Surgeon General Mansell makes the following statement:

“The first case * * * on April 29, was probably imported from India. Once the disease was introduced into such camps as the troops occupied, first at Kahr, and later on at Laram Kotal and bearing in mind the predisposing cause of climate and other conditions of the former place in May, when the men were inactive, the hard work they subsequently underwent, road making, the gradual fouling of the soil through the extension of latrine trenches, inadequate conservancy arrangements due to the want of a sufficient establishment, it is not difficult to account for the rapid spread of the disease. The milk and bazaar supplies were, of course, liable to suspicion but both were under strict supervision, and the outbreak cannot, in my opinion, be attributed to them. The water-supply, which was bad at Kahr, may also be disregarded as the cause, as when the troops moved to Laram, where the supply was excellent, the epidemic increased in violence. I attribute the disease to the fouling of the ground inevitable in camps, the lack of sufficient conservancy establishments, the contamination of food, etc., through the agency of dust and flies, and the necessary crowding, dirt, and intimate contact in which the men lived, often I think carrying infective germs from one to another. The absence of these last conditions goes far to explain the remarkable immunity from the disease that the officers enjoyed.”

Reading the above, one must admit that General Mansell had a fair conception of the agency of flies and of the potency of contact in the dissemination of typhoid fever.

When the English invaded Egypt in 1882, some of the regiments which had been withdrawn from the Mediterranean stations and which constituted a part of the army of invasion, were infected with typhoid fever before leaving their stations. Soon after disembarking at Ismailia occasional cases of typhoid fever began to appear. The disease was at first diagnosed remittent fever, but as it did not yield to quinin in full doses, two autopsies were held and these showed the lesions of typhoid fever. From Ismailia the disease followed the troops until the army took up its permanent camp at Cairo, at which place it culminated in a serious epidemic. The camp sites for the several regiments were situated on the sandy soil and were some distances apart. The latrines were easily dug and regularly filled up. Frequent inspection failed to show any sanitary defect. All excreta from typhoid fever patients, as well as bedding and clothing used by them, were disinfected; the excreta were deposited in a special pit, and all the water was boiled and filtered. Notwithstanding this, many of the hospital corps men contracted the disease in removing the excreta of the patients. On the

march from Ismailia to Cairo the troops drank canal water, but that this water did not occasion the epidemic appears to be borne out by the immunity from typhoid fever enjoyed by the Indian contingency of Seaforth Highlanders, although they used the same water. The Manchester Regiment also, which garrisoned at Ismailia—the termination of the canal—and used this water, had only one case. The Household Cavalry and the Fourth Dragoon Guards, which were in the desert during the whole of the campaign, having hard work, suffering much exposure, drinking bad water, and living in insanitary camps, suffered comparatively little. The Seventh Dragoons and the Nineteenth Hussars remained long in camp at Cairo and suffered greatly, the disease being most prevalent among them during the months of November and December. Undoubtedly contact played a large part in this epidemic.

According to Surgeon Major Tarrant, the epidemic of typhoid fever which prevailed among the English and native troops in the Zulu War (1878-1879) was imported into Fort Pearson from Thring's Post and Saccharine. In regard to the same epidemic, Major Hodgson states:

“Numbers of men came from Fort Chelmsford with remittent simple continued fever, of which a large portion proved to be enteric. In a general way, though a large proportion of the fevers were returned as simple continued, my impression is that nearly all of the cases were enteric of the milder or more severe type. From such inquiries as I was able to institute, I concluded that enteric fever was originally brought from Durban and was carried by the troops to the various stations where it broke out, and that in all cases it was aggravated by the gathering together of a large number of men and cattle and the insanitary state which always accompanies such conditions.”

In speaking of contact infection, we have already said much concerning typhoid fever in the American Army during the Spanish-American War. We think we are justified in reproducing here the conclusions of the Typhoid Commission, because the knowledge gained in this study has had much to do with the marvelous reduction in typhoid fever in armies since that time. The general statements with which the Typhoid Commission concluded its report are as follows:

- (1) During the Spanish-American War of 1898 every regiment constituting the First, Second, Third, Fourth, Fifth, and Seventh Army Corps, developed typhoid fever.
- (2) More than ninety per cent of the volunteer regiments developed typhoid fever within eight weeks after they came into camp.
- (3) Typhoid fever developed in certain of the regular regiments within three to five weeks after coming into camp.
- (4) Typhoid fever became epidemic both in the small encampments of not more than one regiment and in the larger ones consisting of one or more corps.
- (5) Typhoid fever became epidemic in camps located in the northern as well as in those located in the southern states.
- (6) Typhoid fever is so widely distributed in this country that one or more

cases are likely to appear in any regiment within eight weeks after assembling. (7) Typhoid fever usually appears in military expeditions within eight weeks after assembling. (8) The miasmatic theory of the origin of typhoid fever is not supported by our investigations. (9) The pythogenic theory of the origin of typhoid fever is not supported by our investigations. (10) Our investigations confirm the doctrine of the specific origin of typhoid fever. (11) With typhoid fever as widely disseminated as it is in this country, the chances are that if a regiment of 1,300 men should be assembled in any section and kept in a camp, the sanitary conditions of which were perfect, one or more cases of typhoid fever would develop. (12) Typhoid fever is disseminated by a transference of the excretions of an infected individual to the alimentary canals of others. (13) Typhoid fever is more likely to become epidemic in camps than in civilian life, because of the greater difficulty of disposing of the excretions from the human body. (14) A man infected with typhoid fever may scatter the infection in every latrine in a regiment before the disease is recognized in himself. (15) Camp pollution was the greatest sin committed by the troops in 1898. (16) Some commands were unwisely located. (17) In some instances the space allotted the regiments was inadequate. (18) Many commands were allowed to remain on one site too long. (19) Requests for change in location made by medical officers were not always granted. (20) Superior line officers cannot be held blameless for the insanitary condition of the camps. (21) Greater authority should be given medical officers in matters relating to the hygiene of camps. (22) It may be stated in a general way, that the number of cases of typhoid fever in the different camps varied with the methods of disposing of the excretions. (23) The tub system of the disposal of fecal matter as practiced in the Second Division of the Seventh Army Corps is to be condemned. (24) The regulation pit is not a satisfactory method of disposing of fecal matter in permanent camps. (25) In permanent camps where water carriage cannot be secured, all fecal matter should be disinfected and then carted away from the camp. (26) Infected water was not an important factor in the spread of typhoid fever in the national encampments in 1898. (27) To guard against the contamination of the water-supply, troops in the field should be provided with means for the sterilization of water. (28) Flies undoubtedly served as carriers of the infection. (29) It is more than likely that men transported infected material on their persons or in their clothing, and thus disseminated the disease. (30) Typhoid fever as it developed in the regimental organizations was characterized by a series of company epidemics, each one having more or less perfectly its own individual characteristics. (31) It is probable that the infection was disseminated to some extent through the air in the form

of dust. (32) A command badly infected with typhoid fever does not lose the infection by simply changing its location. (33) When a command badly infected with typhoid fever changes its location it carries the specific agent of the disease in the bodies of the men, in their clothing, bedding, and tentage. (34) Even an ocean voyage does not relieve an infected command of its infection. (35) After a command becomes badly infected with typhoid fever, change of location, together with thorough disinfection of all clothing, bedding, and tentage, is necessary. (36) Except in cases of the most urgent military necessity one command should not be located upon the site recently vacated by another. (37) The fact that a command expects to change its location does not justify neglect of proper policing of the grounds occupied. (38) It is desirable that the soldier's bed should be raised from the ground. (39) In some of the encampments the tents were too much crowded. (40) Medical officers should insist that soldiers remove their outer clothing at night when the exigencies of the situation permit. (41) Malaria was not a prevalent disease among troops that remained in the United States. (42) The continued fever that prevailed among the soldiers in this country in 1898 was typhoid fever. (43) In addition to the recognized cases of typhoid fever, there were many short or abortive attacks of this disease which were generally diagnosed as some form of malarial fever. (44) While our examinations show that coincident infection with malaria and typhoid fever may occur, the resulting complex of symptoms is not sufficiently well defined and uniform to be recognized as separate diseases. (45) About one-fifth of the soldiers in the national encampments in the United States in 1898 developed typhoid fever. (46) Army surgeons correctly diagnosed about half the cases of typhoid fever. (47) The percentage of deaths among cases of typhoid fever was 7.61. (48) When a command is thoroughly saturated with typhoid fever, it is probable that one-fourth to one-third of the men will be found susceptible to this disease. (49) In military practice, typhoid fever is often apparently an intermittent disease. (50) The belief that errors in diet, with consequent gastric and intestinal catarrh, induce typhoid fever, is not supported by our investigations. (51) The belief that simple gastrointestinal disturbances predispose to typhoid fever, is not supported by our investigations. (52) In a considerable percentage (a little more than one-third) of the cases of typhoid fever which are recorded as having been preceded by some intestinal disturbance, the preceding illness was so closely followed by typhoid fever that we must regard the former as having occurred within the period of incubation of the latter. (53) More than ninety per cent of the men who developed typhoid fever had no preceding intestinal disorder. (54) The deaths from typhoid fever were 86.24 per cent of the total deaths.

(55) The morbidity from typhoid fever per 1,000 of mean strength was a little less than one-fifth (192.65). (56) The mortality from typhoid fever per 1,000 of mean strength was 14.63. (57) The average period of incubation in typhoid fever is probably about ten and a half days.

In the South African War (1899-1902) the British repeated all the mistakes which we made in 1898, with practically the same results. We have before us two reports of typhoid fever in the South African War from the same source. In one the statement is made that, with a total strength of 557,653 officers and men, there were 57,686 cases of typhoid fever and 8,225 deaths. In the second statement, we are told that the total strength was 380,605, that there were 57,684 cases with a morbidity of 15,115 and a mortality of 2,100 per 100,000. It will be seen that the most important difference in these statements concerns the total strength. We assume that the larger figure gives the total strength of the British Army at that time in all quarters of the empire, while the smaller figure gives the total strength of those who were engaged directly in the South African War.

It is generally stated that in the Russo-Japanese War, typhoid fever was less prevalent in both armies than it was in the American Army in the Spanish War or in the British Army in the South African War. We have not been able to find official figures from either the Japanese or Russian Armies. Vincent and Muratet give the number of cases in the Russian Army as 21,309 and in the Japanese as 5,474, but neither the strength nor the mortality is given. Yagisawa states that the incidence of this disease averaged 500 per 100,000 and the mortality 100 in the Japanese Army. Some have sought to find in these relatively low figures evidence of racial immunity, especially among the Japanese. We are not ready to accept this explanation. The Japanese medical officer had more authority, the line officer had a greater appreciation of medical advice, and camp pollution did not exist to the extent that it did in our camps in 1898.

It must not be understood that the prevalence of typhoid fever in armies has been confined to times of war. Garrisoned troops, certainly in former days, suffered more heavily from this disease than did the civilian population in the city in which or near which the garrison was located. From 1855 to 1869, the annual death rate in the garrison at Munich was more than four times that of the city during the same period. The garrison and the city had the same water-supply and the excess in the garrison was probably due to the greater prevalence of contact infection. The highest incidence and mortality from this disease of which we have record was that which prevailed in the British Army in the Khyber district in India in 1898. The morbidity for this year was 16,050 and the mortality 4,060 per 100,000. The British Army

being scattered over the vast empire furnishes many interesting facts to the student of epidemiology. In 1898 the mortality rate in the civil population of England was 7 per 100,000; among soldiers stationed in Great Britain it was 24; among those at Gibraltar it was 132; among those in South Africa it was 577; among those in India it was 1,000; among those in Egypt it was 2,340.

Before discussing its prevalence in the World War, we shall turn aside and give attention to those studies and advances, the application of which has changed radically the relative importance of typhoid fever in armies. Formerly, it was the disease which army medical officers had most to fear. Now it is that which is most perfectly under control. Formerly, the young civilian who went into the army, whether in peace or in war, greatly increased his chance of being infected with this disease. Now he greatly reduces the chance by this transfer from civilian to military life.

Individual Susceptibility to Typhoid Infection.—All the enigmas in the typhoid problem have not been solved. One of the most interesting of these is the difference in susceptibility to this infection exhibited by individuals. As we have stated, about one-fifth of the soldiers in our national encampments in 1898 developed typhoid fever. Why did four men out of every five escape this infection? To one who visited Chickamauga Park at that time, it would seem that the whole camp was saturated with this infection. The only answer that we could give to this question at that time was that four out of five by lucky chance escaped the introduction of the bacillus into their bodies. We called attention to the fact that in the most deadly charges, when columns of men were facing a fire which apparently should strike down every man, many came through unscathed. At first this explanation quite satisfied us, but on closer study we observed that many individuals who manifested some trifling ailment, often not sufficient to send them to hospital or even to quarters, subsequently proved immune to typhoid. At the time the Typhoid Commission was making its inspection it had no facilities for applying the agglutination test to these individuals. Subsequently in Porto Rico, Reed, chairman of the commission, observed similar instances and did apply this test. He found that in many individuals typhoid fever manifested itself in only slight and transient effect upon the body. These slight attacks gave subsequent immunity. In other words, typhoid fever varies greatly in its effect upon individuals. In some it may be only a slight and transient indisposition, while in others it causes a prolonged and distressing illness, terminating in about ten per cent of the cases in death and often leaving serious complications in those who recover. This, however, is not the whole nor the most interesting part of the story. Denmark reports

that 319 soldiers partook of potato salad which had been prepared by a typhoid carrier. Only 22 of these men developed typhoid fever. The natural inference would be that the infection was not evenly distributed through the food and those who swallowed the specific bacilli developed the disease, but 59 of those who ate of the salad and who were not ill developed the agglutination test, showing that typhoid bacilli had been introduced into their bodies. Furthermore, there were 160 comrades who did not partake of the salad but who were subsequently closely associated with those who did. Of these, five developed typhoid fever, undoubtedly through contact, and 39 others showed the agglutination test. Further still, in the stools of certain of these individuals who did not develop the fever but who showed the agglutination test, typhoid bacilli were found. When typhoid bacilli are found in the stools of those who do not develop the disease, the most reasonable explanation is that the bacilli have found their way into the alimentary canal but have failed to reach the blood current. This explanation will not satisfy, because to develop the agglutination test the bacilli must reach the blood. Moreover, in many such instances typhoid bacilli are found in the urine and they could reach the kidneys only through the blood. Scheller reports an epidemic in which 72 people drank milk contaminated by a carrier. Thirty-two of these developed typhoid fever, but 40 remained apparently perfectly well. In 18 of the 40 apparently well people, typhoid bacilli were found in either the stools or the urine or in both. These and similar instances indicate that typhoid bacilli do not always induce the disease, even when they find their way into the blood. A still more interesting fact is the observation that apparently healthy people may for weeks and months carry the typhoid bacilli in their bodies, eliminate them in their excretions and suddenly, after the organism has been an apparently harmless guest for a long time, they develop the disease. The explanation of these phenomena is not easy. It would seem that typhoid bacilli may exist, grow, and multiply in the human body, living at the expense of the host but without causing any antagonism on the part of the body cells. In other words, it seems that sensitization of the body cells is essential to the development of typhoid fever, and that there are many individuals whose body cells are, at times at least, not susceptible to such sensitization. The facts we are now discussing are not only of great scientific interest, but they indicate how complex is the problem of the eradication of this disease. There should be but little danger of the spread of typhoid fever from the 32 cases who developed the disease in Scheller's report. These were sick in bed and their excretions presumably were thoroughly sterilized, but what of the 18 who were not ill, who

continued to mingle with their fellow men, and who eliminated typhoid bacilli in their feces and urine?

Protection Afforded by a Previous Attack.—Early in the history of this disease, at least after it was recognized as distinct from typhus fever, observations were made indicating that one attack gives the individual permanent immunity. This observation was recorded by Bretonneau as early as 1829, and subsequently confirmed by many French and a few American physicians. However, as early as 1849 exceptions to this rule were recorded. In observations on this point, generally reliance must be placed upon the memory of the patient. Moreover, there is always the chance that the diagnosis was not correct. Notwithstanding these difficulties, it is now generally agreed that even a previous attack of this disease does not give perfect and complete immunity. Some clinicians have reported a relatively large number of cases in which the disease has at least twice attacked the individual. In 666 cases of typhoid fever, Eichhorst found a history of previous attack in 4.2 per cent. Osler placed the figure in his experience at 2.2 per cent. It must be borne in mind that these figures were obtained before we knew anything of the paratyphoid fevers, and no one is able at the present time to give anything like an exact estimate of the number of cases in which any one of the group of typhoid fevers has recurred. It is safe to say, however, with a good deal of certainty, that one attack of any one of the group does not give absolute immunity to a subsequent attack by the same specific microorganism. In other words, the protection furnished by one attack of the disease, whether it be Eberthian, paratyphoid A, or paratyphoid B, does not give absolute protection against the subsequent development of the same typhoid fever. Certainly, all bacterial immunity is relative. This is especially true of such a disease as typhoid fever in which the infecting dose is subject to such wide variations.

It is a widely held belief that many people acquire a partial immunity of typhoid fever by frequently swallowing small numbers of the bacilli. If a city has had for a long time an infected water-supply, newcomers to that locality are more prone to develop typhoid fever than the natives. This statement is not founded upon scientific data, but it does rest upon repeated observation and is altogether reasonable. It is believed by some that the lessened susceptibility to this disease which comes with age is, in part at least, due to protection secured in this way. It is generally stated that physicians and nurses are less susceptible to the disease than others. However, Gay states that typhoid fever occurs eight times as frequently among these people as it does among those who do not come into such intimate contact with the disease. The physician or nurse may acquire a certain degree of immunization by frequent

absorption of small numbers of typhoid bacilli, but this immunity will disappear when massive doses are absorbed.

Vaccination against Typhoid Fever.—In 1896, Wright, then a professor in the British Army Medical School, began to practice vaccination against this disease. He grew typhoid bacilli in bouillon for three weeks, killed the bacteria by heating to 63° C., and preserved the preparation by the addition of .5 per cent phenol. He developed a method of computing the number of bacteria by comparing the suspension with a given dilution of red blood cells. The dose he employed was from 750 to 1,000 million. The injection is made subcutaneously and muscular penetration should be avoided. Wright gave only one injection. He vaccinated troops going to India. The procedure was wholly voluntary, and in no instance did he succeed in inducing all the men in any organization to submit to vaccination. The vaccinated and the unvaccinated were mixed in the same organization. It happened at times that those organizations which were most thoroughly vaccinated were sent to the most highly infected districts. Notwithstanding these facts, the figures showed on the whole that the mortality among the vaccinated was much less than among the unvaccinated; in fact, even when tried in this inadequate way, both the morbidity and mortality were reduced to half. As indicated above, it happened that certain regiments largely vaccinated, sent to India and placed in badly infected localities, showed a higher mortality than unvaccinated troops in less infected stations. This apparently discouraged even Wright, and he suggested that there might be a "negative phase" immediately following vaccination in which susceptibility to the disease may be increased. For some years much was said pro and con concerning this so-called "negative phase," but we have long since concluded that there is nothing to it. When the South African War came on, it was expected that vaccination against typhoid fever would be thoroughly tested and definite results one way or the other obtained, but the procedure had apparently not won the confidence of British medical officers and the South African War, with its high death rate from this disease, passed into history and the world knew no more about the value of typhoid vaccination than it did before; indeed, in 1903 antityphoid inoculation in the British Army was officially prohibited and this prohibition continued for about 18 months. Fortunately, Wright's procedure was vindicated by the College of Physicians and again put into operation. It grew in favor, and, although it was not made compulsory until the World War, in 1910, 82.3 per cent of British soldiers in India had received the treatment. From 1906 to 1910, with increasing vaccination, the morbidity rate in India fell from 15.6 to 4.6 per cent, and the mortality from 3.19 to 0.63 per cent.

Russell, of the United States Army, having carefully studied vaccina-

tion as practiced in the English Army, succeeded in having it made compulsory in our army in 1911. This was the first army in which typhoid vaccination was made compulsory, and the result which has followed has justified the wisdom, persistence, and scientific skill of Colonel Russell, who had charge of this matter. In 1902, with no vaccination, the number of cases per 100,000 in our army was 699. In 1913, with compulsory vaccination well established, the corresponding figure was 4.4.

In 1911, French soldiers occupying certain garrisons in France, in

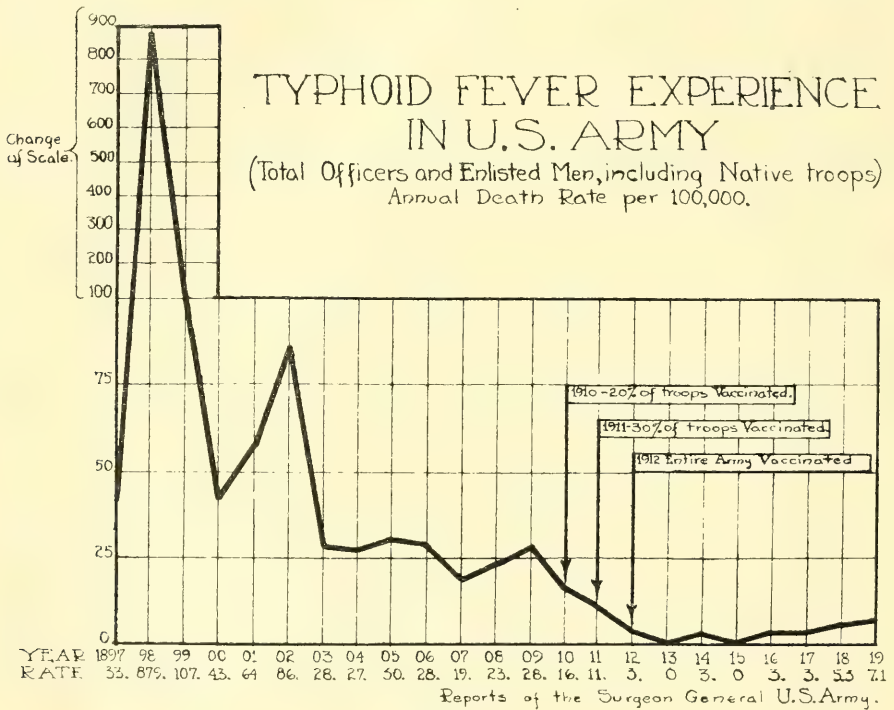


Fig. 26.

Morocco, and in Algiers, were vaccinated, but compulsory vaccination did not take effect until the World War began, and then so rapidly were French civilians pressed into service, or to speak more truly, so rapidly did French civilians flock to the service, that universal vaccination was not at the time possible. The French had been convinced by their experiments in the vaccination of certain garrisons of the value of this procedure, so that there was no question about making it compulsory as soon as possible after the war began. Rist states that in 1916 only 73.9 per cent of the French Army had been vaccinated against typhoid fever.

In the war with Tripoli (1911-1912) the Italian Army was partially vaccinated. At this time French and German vaccines were employed and the former found to be much more efficient. In the Russian Army typhoid vaccination was not made obligatory until 1915, and during the war vaccines were prepared in various laboratories, sent to certain places where they were tested, and then used on the soldiers. The vaccines employed in the Russian Army are those prepared according to the directions of the Pasteur Institute of Paris.

Vaccination apparently was first tried in the German Army in the war against the Herreros in Africa (1904-1907). According to Kuhn, among 7,287 vaccinated soldiers in this war, typhoid morbidity was 5,100 and mortality 330 per 100,000, while among 9,209 nonvaccinated men the morbidity was 9,900 and the mortality 1,260 per 100,000. It will be seen from these figures that the morbidity among the vaccinated was a little more than one-half and the mortality among the same a little more than one-fourth what it was among the nonvaccinated. While these figures demonstrated the value of typhoid vaccination, they were not altogether satisfactory and left room for doubt and discussion as to the value of the procedure. For some years thereafter those who had in charge the health of the German Army relied for protection against typhoid fever on sanitation and the elimination of typhoid carriers. It is an interesting fact that without vaccination and through rigid execution of the above mentioned methods, mortality from typhoid fever in the German Army was reduced to about three in 100,000 in 1912. From the best information we can obtain, it seems that compulsory vaccination against this disease was not established in the German Army until the late fall of 1914 and not until several thousand cases of the disease had developed.

The preparation of the vaccine has varied in different countries and from time to time. As we have stated, Wright first killed the bacteria at 63° C. There has been much discussion concerning the influence of temperature used in sterilizing the cultures on the protective value of the bacilli. Most bacteriologists have held that the lower the temperature, provided it secures complete sterilization, the better the vaccine. In consonance with this view, the tendency has been to lower the point at which sterilization is secured. In most laboratories the temperature now used varies from 53 to 56°. It seems to make but little difference whether the bacilli are grown on solid or in liquid cultures. When grown on the former the growths are removed and suspended in a physiologic salt solution. Experimentally, some investigators have killed the bacilli with chemical agents, thus avoiding heating. Ether and alcohol have been used for this purpose, but there is no convincing evidence that the vaccines prepared by these methods

are more efficient than those which are sterilized by heat. In a few instances, the addition of phenol alone has been depended upon to kill the bacilli. Moreover, iodine and sodium fluorid have been advocated, but the vaccines now generally employed, both in military and civil life, consist of typhoid bacilli sterilized by heating to from 53 to 56° C.

At first only one administration of the vaccine was employed, but it was found that repeated vaccination apparently increased the degree of immunity. In the American Army at the beginning of the World War three doses were administered at intervals of about seven days. In the French Army four injections have been recommended, but it has been quite impossible to secure this number in all instances. Gay, who has investigated this matter thoroughly and has had much experience himself in administering various vaccines, makes the following statement:

“The doses employed in immunization have varied in the hands of different experimenters and have, in general, tended to increase in number and amount of bacteria employed. Whereas the first advocates of typhoid immunization, Wright, Pfeiffer, and Kolle, used only one or two injections, the number has subsequently been increased by most observers to three or four. The size of the dose is generally increased on successive inoculations, beginning with a dose of 125 to 500 million of bacteria, which are estimated by one of several methods; by counting the bacteria in a blood-counter, by comparison with red blood-corpuscles, or better still, by utilizing weighed amounts of dried bacteria. The most frequent doses that have been used when three inoculations are given have been 500, 1,000 and 1,000 million, but the total number of bacteria injected throughout the course of treatment would seem to be more important than the number of injections (Vincent and Muratet, Landouzy). Vincent estimates that at least 2,000 million should be used in a course of treatment, and the number of injections may be diminished from the four which he originally advocated to two, provided the total number of bacteria injected remains the same. In the British Army up to the time of the World War it was customary to give only two doses of vaccine, which were increased to three in the American Army with distinctly better results. We understand that the number of injections has since been increased to three in the English Army as well. In France four and even five injections have been given, or, as mentioned, the same amount in two or three injections. We personally have recommended three injections of 800 million bacteria or one-tenth of a milligram, but have recently been led to advocate increasing the number of injections to four or the size of each dose, owing not only to the occurrence of a few cases of typhoid among civilians that had been vaccinated, but also to the failure to obtain a positive typhoidin test after three vaccinations in a few cases, although it almost invariably has appeared when the fourth injection was subsequently given.”

There has been some discussion as to the time allowed to elapse between injections. It is customary to make the injections at intervals of about seven days. This period has been selected, because it is believed to represent the time necessary for the maximum formation of antibodies. Gay is quite right in claiming that the antibodies are in themselves no

measure of the degree of protection, and he holds that there is no reason that the inoculation should not be given every second or third day instead of the longer period of seven days. However, where large bodies of men are inoculated as in armies, some will develop more or less marked symptoms and the period of seven days allows ample time for recovery from the effects of the previous inoculation.

The symptoms following antityphoid inoculation are both local and general. When the inoculation is made subcutaneously, as it always should be, and under proper precautions, consisting in the sterilization of the surface, the local symptoms are generally confined to slight swelling with more or less pain and redness extending usually only a few centimeters from the point of injection. The general symptoms may embrace malaise, dizziness, headache, possibly vomiting, and elevation of temperature, which seldom goes above 102° F. In our army it has been the practice as soon as a squad of men arrives at camp to send them to a large building where all are stripped and subjected to examination by the various specialists. After receiving these examinations the men pass in line before medical men who vaccinate for smallpox and administer the inoculation for typhoid fever. The men are then instructed to don their uniforms and no duty is required for the remainder of that day and the following day. On the day after vaccination the arms of all men are inspected. No serious local effect has been known to occur, even when the swelling persisted for some days, and in extreme cases when a noninfected abscess occurs, the recovery from the local effect is prompt and without any serious complication. In general the second and third injections, possibly on account of the larger amount of vaccine used, give rise to more marked symptoms than the first. In civil life, certain organic diseases, such as arteriosclerosis, diabetes, nephritis, myocarditis, pleurisy, and chronic tuberculosis, should be regarded as contraindications to typhoid inoculation. It will be understood that in the army these diseases have been excluded before the inoculations are made. It has been held by Besredka and confirmed by Gay and others, that sensitized vaccines produce less marked symptoms and are quite as efficient as others in giving protection. By sensitized vaccines we mean typhoid bacilli which have been subjected to the blood of animals immunized to typhoid bacilli, subsequently washed with physiologic salt solution, and then killed by proper temperature.

Gay defines a slight local reaction as redness of the arm of from 40 to 75 mm. in diameter; a severe local reaction as redness of the arm over 75 mm. in diameter; a slight general reaction as headache, lassitude, disturbed sleep, loss of appetite, and rise in temperature to 38° C.; a severe general reaction as chill, diarrhea, and rise in temperature above 38° C. Force, using sensitized vaccines, found in 4,845 inocula-

tions that slight local reactions were produced in 12 per cent, severe local reactions in 3.6 per cent, slight general reactions in 24.5 per cent, and severe general reactions in only 2.4 per cent.

It is customary to measure the effect of typhoid inoculation by the development of antibodies in the blood, the agglutinins, the lysins, the tropins, and the fixation antibodies. Generally, the development of agglutinins in the blood is the one thing relied upon. It has been assumed that these antibodies measure the protective effects of the inoculation. We hold with Gay that this assumption is without warrant, while we admit that it is the only practical measure we have. The development of agglutinins is, as was first held by Widal, who discovered this phenomenon, a reaction of infection and not one of immunity. The typhoid patient during the course of the disease develops agglutinins at a time when he is certainly not immune to the disease. After his recovery the agglutinins in his blood gradually decrease and disappear within a few months at most. After their disappearance the man is in the highest state of immunity to this disease that can ever be induced in the body. The scientific explanation of the action of typhoid inoculation is, in our opinion, cellular and not humoral. By the introduction of dead typhoid bacilli the body cells are taught and trained to destroy these organisms. A new function in the body cells is developed and the cells pour out new secretions which are antagonistic, specifically antagonistic, to typhoid bacilli. Subsequently, when a few of these organisms find their way into the body, the cells, already trained so to do, pour out their specific secretions and destroy the invading organisms before they have time to multiply sufficiently to induce the disease. The presence of agglutinins in the body occurs at a time when the body cells are being trained to destroy the bacterial cells. After this function of the body cells has been fully developed and there are no longer typhoid bacilli in the body, the agglutinins gradually disappear from the blood.

Gay and his associates have attempted to develop a method for determining the degree of immunity to typhoid bacilli possessed by individuals. For this purpose they have used typhoid bacilli precipitated from glycerin bouillon cultures. These are washed in alcohol and ether, dried, and kept in sealed tubes. This material, which they have called typhoidin, is mixed with a small amount of carbolated salt solution and applied with a sterile toothpick to a minute abrasion of the epidermis. A local reaction follows, and this is compared with the reaction induced in another small abrasion on the same individual to which typhoidin is not applied.

“A positive reaction consists in the presence after 48 hours of a definite indurated papule surrounded by a reddish areola of at least five millimeters. With the test in its present form Gay and Lamb obtained positive results in seventy-five per

cent of cases of recorded typhoid, who had suffered from the disease from two to twenty-two years previously. Normals with no history of typhoid or typhoid vaccination gave positive results in a little over fourteen per cent."

It is highly desirable that this method of testing relative individual immunity to typhoid infection should be developed. It would supply a means of determining in a practical way the effect of typhoid inoculation in individuals. Of course, it will be understood that the typhoidin test is in no way concerned in inducing immunity to this disease. On the other hand, it offers a practical method of determining to what extent the inoculation has been efficacious.

With the discovery of the paratyphoids and the realization of the fact that immunity to one typhoid fever does not give at least equal protection to other typhoid fevers, it became necessary to vaccinate not only against Eberthian typhoid, but against paratyphoid A and paratyphoid B as well. To separately vaccinate against each of these typhoids, giving three inoculations for each, would be to impose greatly increased labor on the medical officer and multiply the discomfort of the vaccinated. It was, therefore, decided to mix the vaccines and give all forms in one dose. This is the method now generally employed, each inoculation consisting of at least 500 million Eberthian bacilli and 250 million each of the paratyphoids. Neither the local nor the general symptoms are intensified by this increase in the number of bacteria administered at one time. Preparations containing the bacilli of the three typhoid fevers are known as triple vaccines, and in our army these vaccines are administered three times at intervals of about seven days. Each vaccination is recorded on a card which the soldier carries, showing the date, place, and the administrator for each injection. It is believed that this has been carried out so thoroughly that practically none of our soldiers went to France without receiving three administrations of the triple vaccine. As the war progressed, however, a method of administering the three doses in one was sought and the so-called lipo-vaccine resulted. This preparation consists of the mixed bacilli in number equal to that previously given in three injections, suspended in oil, and given in one injection. It was believed that the oil suspension would be more slowly absorbed, the body cells would be more gradually supplied with this foreign material, and their education in the development of antibodies would be more complete. It was found, however, that it is much more difficult to sterilize bacteria suspended in oil than when suspended in saline solution. There is no evidence that the lipo-vaccine did any harm or that it was less effective than the saline suspension, but on account of the uncertainty in sterilization the use of the lipo-vaccine has been discontinued.

While vaccination has been a most potent factor in the control of

typhoid fever, especially in armies as shown by comparing the records of the World War with those of previous wars, it has not wholly eliminated this disease. Taking our own army and comparing it with the same organization in 1898, the medical officer in attempting to control typhoid fever has in the World War possessed three factors which he did not have in 1898. In the first place, he has had more authority and he has had more intelligent line officers with whom to deal. At Chickamauga in 1898, a Major General went ostentatiously once a day and drank from a well which had been condemned by his own medical officer. In the World War, line officers, especially those of superior rank, were at all times willing to listen to advice given by medical officers, and we know of no instance in which such advice was not followed, provided it was sound and feasible. In the second place, in 1898 every camp in the United States occupied for a few weeks or longer was grossly polluted. In the World War there was no camp in the United States, the sanitation of which could be condemned. Improvements in methods of water purification, especially in filtration and chlorination, have been powerful factors in reducing the morbidity and mortality from enteric disease, notably typhoid fever and dysentery. In the third place, vaccination against typhoid fever has so far increased the soldier's resistance to this disease that he does not succumb to it except in cases of massive infection. We have no doubt that these conditions have prevailed in all the great armies engaged in the World War.

Unfortunately, some medical men, especially was this true of some of our medical officers in France, believed that vaccination gives absolute immunity to typhoid fever, and consequently it happened that they failed to recognize the disease when it occurred among the vaccinated. It is a fact that in some of the organizations in France this disease was not correctly diagnosed until the autopsy was made. We have seen that even one attack of this disease does not give absolute immunity to subsequent infection. How, then, could we expect that vaccination should furnish absolute protection? Vaccination against typhoid fever is a most potent factor in the eradication of this disease, but as a distinguished French epidemiologist has stated, it raises a barrier which, however, is not insurmountable. It would be a great misfortune indeed if either the medical profession or the laity should get the idea that vaccination does away with the necessity of sanitation.

A few medical men first fancied that they saw in cases of typhoid fever among the vaccinated, a modified and less virulent form of the disease. In every epidemic, as we have already pointed out, there are many mild cases; in some more, in others less. More thorough and scientific study of typhoid fever among the vaccinated shows that in no particular does the disease among these men, when it does occur,

differ from that which manifests itself among the unvaccinated. The death rate in the two groups, while varying greatly in different epidemics, is the same. The complications, relapses, sequelae, are in no way different in the two groups.

The late Major V. C. Vaughan, Jr., who collected data on typhoid fever in the A. E. F., made the following statement regarding this disease as it developed in the vaccinated:

“(1) Study of 270 cases infected with *Bacillus typhosus*, all of whom had received triple typhoid vaccine, leads us to conclude that in those hospital cases, the clinical picture of typhoid in the vaccinated was similar to that of the unvaccinated. Absence of leukocytosis, continued fever of the usual course and duration, rose spots, palpable spleen, relapses, and complications, all remained characteristic of the disease. (2) In our series the mortality was eleven per cent. (3) Positive cultural results from blood, urine, and feces were of about the same percentage as in nonvaccinated cases, and the duration of the bacteremia appeared to be the same. (4) Cases infected within eight months after vaccination had an average severity (fatal percentage combined with ‘severe’ percentage) of under ten per cent. After eight months the severity percentage gradually increased. Our figures for later months are not complete enough to allow us to draw conclusions as to the period of maximum immunity. (5) The onset of the disease was more frequently acute when occurring within the first month after inoculation. (6) Sixteen cases with onset from seven to twelve days after inoculation (the usual incubation period) were probably infected during the interval after inoculation. (7) The paratyphoid infections, although much milder as a group, could not be clinically distinguished in individual cases from straight typhoid. They were of much less frequent occurrence than was the latter. (8) It is probable that a large number of vaccinated individuals were infected with *Bacillus typhosus* and allied organisms who never became sick enough to require admission to hospital. In these the immunity mechanism was eventually successful in combating the infection so that they did not develop clinical typhoid fever. Their epidemiologic importance is recognized. This report deals with the remaining cases—those who in spite of vaccination developed the disease. (9) Six possible causes of failure of vaccination to protect against typhoid are discussed, particular emphasis being placed on a new clinical variety, called for convenience ‘backhanded’ typhoid. (10) The incidence of the typhoid group of diseases in the A. E. F. was less than 0.1 per cent as compared with twenty per cent for the Spanish-American War.”

Typhoid Fever in the World War.—It is too early to even attempt a detailed history of this disease in the great war so recently ended. Trustworthy reports from many armies are still lacking. The contrast, however, in the prevalence of the disease in this war compared with its ravages in past wars is so striking that general statements may be made now, provided permission is given to fill out details later. The best report that has come to our hands concerning typhoid fever on the Western Front is from Goodall of the British Army, who has written on “Enteric Fever in Flanders.” He states that this disease was prevalent, however not widely so, in Belgium at the time of the German in-

vasion. The swift advance of the Teuton hordes, the great desolation which they wrought, and the economic straits into which the Belgians were suddenly thrown, all were favorable to the rapid development of this disease. Besides, the part of Belgium west of a line drawn through Antwerp and Brussels, was thickly populated and highly cultivated, furnishing abundant human excreta, which was used largely for the purpose of fertilization. The water-supplies of villages and small towns were mostly from shallow wells. In the fall of 1914, there were four armies in Flanders, the British, French, and Belgian on one side and the German on the other. Of these armies the only one adequately vaccinated was the British and up to that time it had employed only the Eberthian vaccine. According to Bruns, there were 20,000 cases of typhoid fever in the German Army during the winter of 1914-15, and according to Goldscheider and Kroner, the disease became epidemic in this army on the Western Front in September, 1914, and reached its height in November of the same year. Goodall states that there were somewhere about 4,000 cases under treatment daily during January and February, 1915, in Dunkirk and its neighborhood. Of Belgian civilians 1,000 cases of typhoid fever passed through the hospitals in Ypres and Poperinghe, while more than 1,000 more were cared for in their homes. The British Army furnished 827 cases up to May 22, 1915. British medical officers had charge of the epidemic, especially among the Belgian civilians, established laboratories, purified the drinking water, visited the homes, and fed the people. Vaccination, even among the civilian population, was made compulsory. However, examination at the laboratories soon showed that a large percentage of the cases were paratyphoids. For this reason, Goodall is inclined to attribute the success in eradicating the disease to sanitary measures rather than to vaccination. It is generally believed, and probably is true on the whole, that the paratyphoids are less severe than Eberthian infection, but at one of the hospitals established by the British, 9.7 per cent of Eberthian cases and 19.2 per cent of paratyphoids died. In another hospital, the mortality among the paratyphoids was only 2.1 per cent, while that among the Eberthian cases was 20.9 per cent. A very urgent question was the water-supply. That of Ypres was good before the war. The water tower remained undamaged up to April, 1915, but the mains were in part destroyed by shells. In January, 1915, the burgomaster ordered the boiling of all water used for drinking purposes. The English, however, cleaned a public swimming bath and used this as a storage tank for drinking water. Water from adjacent moats, undoubtedly infected, was treated with hypochlorite of lime and turned into the tank from which it was pumped into barrels and distributed. From 45,000 to 75,000 litres were purified and distributed daily. Chlorid of lime was

furnished to householders, together with a spoon-measure and a printed card of instructions for additions to water. Eighteen hundred householders were supplied in this manner in Poperinghe and nearby villages. Searching parties were sent out and went from house to house seeking cases of typhoid fever. When found, patients were sent to hospital and other members of the family vaccinated. About 6,500 houses were inspected during a period of four months. So thoroughly was this work done that there was no recrudescence of the disease in the region about Ypres and Poperinghe during the continuance of the war. It is probably of sufficient epidemiologic interest to quote briefly from Goodall, the following:

“Searching parties were formed; each party consisting of a doctor, four volunteer orderlies, four interpreters, two motor ambulances with drivers. The search was conducted systematically, street by street, house by house. Cases of enteric were removed to hospital, unless they could be safely left. The sanitary condition was examined and investigation made as to the water and food supply. Inoculation was brought to the notice of the inmates and urged upon them. For each house a card was filled up, giving the results of these inquiries, which was handed in to local headquarters of the unit the same evening so that a card-index could be kept. A distinctive mark was placed on the door of the house for the benefit of the sanitary squad, R. A. M. C., who followed the visits of the searching parties. The searching parties were working under the supervision of the sanitary officer and reports as to the discovery of cases of enteric, the sanitary state of the premises, etc., were regularly furnished. The sanitary squad undertook the disinfection and cleansing. In Ypres, at any rate, a local contractor emptied the cesspits and disposed of the contents by burning or burial in fields away from the house, and executed repairs. * * * If we want to attribute the (successful) result to any human agency, I should attach more importance to the factors produced by the unusual sanitary measures than to the inoculations, because the inoculations were against infection by *Bacillus typhosus* and not against infection by *Bacillus paratyphosus* A and B. * * * I expected an epidemic in the winter of 1915-1916 at any rate, in spite of the care that had been taken as regards water-supplies and sanitary precautions generally, because if ever a soil was saturated with the poison of enteric, it was that of Flanders in the winter of 1914-1915 and the following spring; but so far as my knowledge goes there has been no enteric worth mentioning in that region since the epidemic which I have discussed.”

We have not been able to find any detailed report concerning the prevalence of typhoid fever in the English Army on the Western Front for the whole period of the war. We do find that in 1915 there were 594 cases and in 1916, 893. It generally happens during a war that typhoid fever increases in the civilian population at home on account of its spread by returned sick and wounded soldiers. This apparently did not happen in England. The number of cases of this disease in England before and during the war is indicated by the following figures:

1911—13,852	1914—8,778
1912— 8,386	1915—6,364
1913— 8,263	1916—5,564

It will be seen from the above figures that, on the whole, there was an actual decrease in typhoid fever among the civilian population of England during the War. We do not have the figures for 1917 and 1918.

Further than the statement already made that 20,000 cases of typhoid fever appeared in the German Army during the winter of 1914-1915, we have only the general statement that during the first year of the war 5.6 and during the second year 1.4 per 1,000 in the German Army were afflicted with this disease. We suppose that these figures refer to the prevalence of the disease on both the Eastern and Western Fronts. Taking them as they stand, they indicate greater prevalence of this disease in the German Army than in either the French, British, or American Armies.

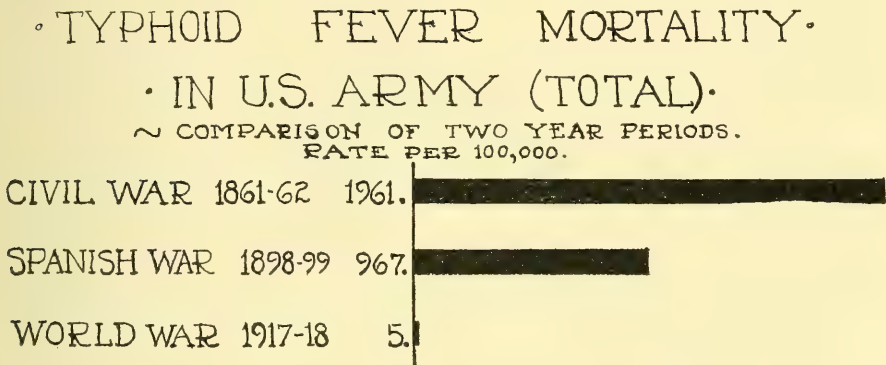
Thanks to Vincent, we have a fairly complete history of typhoid fever in the French Army during the whole period of the war. As has been stated, the French were mobilized so hurriedly that complete vaccination was at first impossible. In November, 1914, an epidemic of this disease appeared in the French Army in the region of Belfort. It spread rapidly from the Swiss border to the sea and became alarming in December, 1914, and January, 1915, when it reached a maximum of 7.24 per 1,000. Systematic and thorough vaccination was begun during this period. In February, 1915, the figure had fallen to 4.38 per 1,000. In March it was 2.49; in April 1.6; in August 2.37; in September 2.65. In February, 1916, there was not a case of typhoid fever in the French Army. From January to August, 1917, the following figures show the prevalence of typhoid fever in the French Army per 1,000 men:

January	—	0.106	May	—	0.036
February	—	0.048	June	—	0.064
March	—	0.026	July	—	0.068
April	—	0.028	August	—	0.063

Vincent states that for the months from November, 1914, to January, 1915, 678.6 men had typhoid fever and 98.6 died out of every 100,000 men. He estimates that if this rate had continued during the 38 months of actual hostilities there would have been in the whole French Army of between four and five million men not less than one million cases and 145,000 deaths. He states further that compared with the morbidity and mortality rates in the whole French population before the war, the morbidity from this disease in the French Army was one-seventh and the deaths about one-eighth of what they were in peace times. From August 3, 1914, to September 1, 1917, the laboratory at Val de Grace

sent to the front 5,513,073 doses of vaccine to be used on the soldiers. No greater argument could be advanced to show the value of typhoid vaccination when universally used. Without this aid it would have been impossible for the French Army to have continued in action. After reading this, will any one say that preventive medicine did not prove a potent factor in winning the war?

The records of our own army are still more gratifying, because as we have already stated, no soldier went from this country to France without the protection afforded by typhoid vaccination. The Surgeon General of our army in his annual report for the fiscal year ending June 30, 1919, makes the following statement:



Report of Surgeon General U.S. Army Vol. 1, 1919
Page 1009.

Fig. 27.

“With the same admission rates for typhoid fever in 1917-1918 as in 1861-1862, there would have been 226,001 cases and 62,694 deaths; and with the same rates as in 1898-1899, 291,637 cases and 30,916 deaths. As it was, there were 1,083 cases and 158 deaths. At no time during the year was typhoid fever of any serious importance except during the latter part of the year 1918 in France. A number of cases appeared among the troops which had been operating and rapidly advancing over battle swept areas in heavily infected territories. That the artificial immunity of a greater number of men did not break down is, indeed, a cause of congratulation and an evidence of the high protective immunity conferred by the typhoid vaccination. * * * It is exceedingly gratifying to note that for that part of the army stationed in the United States and for all the men passing through the camps in the United States during the year 1918, there were only 240 admissions for enlisted men and officers. The mean annual strength was 1,381,429. The annual rate does not, however, give a true picture of the susceptible material, for approximately 3,000,000 men passed through the camps during the course of the year, and it was from this number of men that the 240 cases were drawn. The actual admission rate for the United States however, was 0.17.”

The final figures for the entire war period, kindly furnished us by

the Surgeon General are: Total officers and men in Army, including native troops, 4,128,478; total cases typhoid fever, 1,529; total deaths from typhoid fever, 227. Expressed as a ratio this means that for every 100,000 men there were 37 cases and 5 deaths from typhoid fever. Stating this in another way, there was one case of typhoid among 2,700 men and one death among 18,200 men.

It will be of interest to briefly review one or two instances in which vaccination did fail on account of massive infection. On June 15, 1918, a company of 248 men left Camp Cody, at Deming, N. M., en route for Europe. One of these men was ill at the time of departure and subsequently was found to have typhoid fever. At Meridian, Miss., the train stopped and the men were allowed to bathe in a small lake. Many of them, including the sick man, availed themselves of this opportunity. The drinking water on the train was stored in a barrel placed on the platform of the mess car. Into this barrel men dipped their cups and drank the water, and at the same time immersed their hands more or less. There were, therefore, two opportunities for massive infection, one by the possible discharge from the bowels of the sick man into the lake in which the men bathed, the second in the water in the barrel into which carriers probably immersed their hands. Out of the 248 men, 98 developed Eberthian typhoid fever, with a case mortality of 13.15 per cent. All of these men had received three inoculations with the triple vaccine.

In the spring and summer of 1918, 18 men at Camp Gréene, located near Charlotte, N. C., developed typhoid fever. This disease was prevalent at Charlotte during the same time and all of the sick men visited Charlotte and partook of food in its restaurants and ice-cream parlors. There can be no doubt that at least some of these men acquired the disease in Charlotte. It is possible that others were due to contact. Most of the cases that developed in the United States were among those who reached camp already infected and too late for the vaccination to avert the disease. At Camp Shelby, among eight cases; four had received no typhoid inoculation, two only one dose, and two had had two inoculations. Among the few cases which developed at Camp Gordon, it was shown that in every instance the individual brought the infection to camp. There was a higher rate of this disease in the small camps than in the larger ones. In the latter, the men found everything they required or desired to eat in the camp, where food and drink were protected against contamination. In the smaller camps the men were more likely to eat and drink in the neighboring villages, where there was no adequate protection of food and drink against contamination.

During the summers of 1917 and 1918, typhoid fever was widely distributed over several areas in which camps were located. These facts

prove conclusively that, even when protection is afforded by vaccination, one cannot with impunity disregard possible infection of food and drink.

In France, the most serious infection in our army occurred in a division in an advanced area where the retreating enemy had left the soil and water heavily polluted and where for a time the men were compelled to drink water from shell holes and wherever else found.

In our navy during the year 1918, there were 83 cases of typhoid and paratyphoid, resulting in 9 deaths. The admission rate was 0.16 per 1,000, the death rate 1.78 per 100,000, and the case fatality rate 10.84 per 100. The Surgeon General of the navy in his report for 1919, makes the following statement:

“Typhoid fever has been present and even prevalent in many communities surrounding naval stations and in many places to which men go on liberty and leave. Also the vast majority of the enlisted personnel are within the age period which shows the greatest incidence of the disease. Nevertheless, the admission rate remains very low and the death rate far below the death rate for typhoid fever in the registration area of the United States, which in the year 1917 was 13.4 per 100,000.”

It must be evident that if sanitation and vaccination could be carried out as universally and as thoroughly in our civil population as has been done in our army and navy, typhoid fever would soon become a rare disease among us.

It was feared by some that antityphoid vaccination might render the soldier more susceptible to other diseases, especially pneumonia. Some medical officers held this suspicion, and consequently typhoid inoculation was for a time withheld in certain organizations in one camp. It turned out, however, that there was no more pneumonia among the vaccinated than among the unvaccinated men.

The Eradication of Typhoid Fever.—The great reduction in the prevalence of this disease already secured, and the means by which this has been accomplished, should encourage us and point out a way for the complete eradication of the disease. Since man is the only animal that has typhoid fever naturally and since this disease is transferred from one man to another only by the transference of the excretions of the infected to the alimentary canal of the uninfected, it is plain that we shall cease to have typhoid fever when we cease eating and drinking the excretions of one another. The excretions of recognized cases of typhoid fever should be thoroughly disinfected before they are disposed of. The bedding and clothing of the infected man should be likewise thoroughly disinfected. The floor and furniture of the room which he has occupied should be cleansed with rags soaked in solutions of bichlorid of mercury (1 to 1000), dilute carbolic acid water (2.5 per cent), or dilute solutions of chlorin or chlorinated lime.

Physicians and nurses in administering to patients with this disease should wear aprons of washable material, which should cover the entire front of the body. They must disinfect their hands in sublimate solution, dilute carbolic acid, or chlorin-water, and afterwards wash them with soap and water. The sputum of the patient should be received in paper cups and burned. All these things the intelligent physician and nurse know.

As we have pointed out, the greatest danger in the dissemination of this infection is not from the sick man but from the excretions of the typhoid carrier, and since we do not know who are typhoid carriers we must provide against taking into our alimentary canals the excretions of any human being, it matters not how long and circuitous a route these excretions have traveled from the infected to the uninfected. All handlers of food in hotels, restaurants, and other public eating places, should be periodically examined to ascertain whether or not they are carriers. Moreover, every individual in an infected district should be regarded as a carrier.

The eradication of the paratyphoids presents some difficulties not met in dealing with the Eberthian organism. With the last-mentioned organism, the infection of food or drink is either directly or indirectly from some infected person. The Eberthian bacillus is not known to multiply in any of the lower animals, while the paratyphoid bacilli may and do multiply in the intestinal canal of many domestic animals, such as the dog, cat, rabbit, pig and chicken. According to some, oxen and sheep should be added to this list. In dressing animals for food, paratyphoid bacilli in the intestines may be spread over the meat and may infect those who eat it. Food infection is frequent, especially with paratyphoid B. This organism produces in the animals a soluble poison and immediately after eating the infected food there often is a severe diarrhea, which is likely to persist for some days, and instead of ending in recovery gradually develops into paratyphoid fever. Many instances of food poisoning of this kind have been reported and many more have occurred without being reported.

The paratyphoid organisms are much more resistant to external agencies than is the Eberthian bacillus. The former not only live for a longer time outside the animal body, but they are undoubtedly capable of multiplication, especially in decomposing meat. The relative geographical distribution of the various forms of typhoid fever is a matter of epidemiologic interest. Before the War it was well known that the paratyphoids were widely prevalent in Germany. It was also known that these forms were abundant in oriental countries. It appears that both the Germans and the oriental contingents to the allied armies infected a large part of France with the paratyphoid virus. It is possible that the movements of soldiers

in the World War will materially change the relative geographical distribution of these forms of typhoid fever. There were about 260 cases of paratyphoid in our army on the Mexican Border in 1916. Up to that time vaccination had been against the Eberthian bacillus only.

Drinking waters used in this country are (a) cistern waters, (b) surface waters, (c) subterranean waters. Cisterns are reservoirs into which water falling on the roofs of houses is collected. The cisterns or reservoirs in the northern states are invariably under ground to prevent freezing. In some of the southern states they are built above ground. The purity of cistern water depends upon the cleanliness of the roof upon which the rain falls, the conductors which lead to the reservoir and the possibility, especially in underground cisterns, of leakage into the reservoir. Cistern waters are used only for individual families. The water is often highly contaminated with organic matter and rich in bacteria, but seldom is it specifically infected. Family epidemics of typhoid fever have been frequently observed and have been found to be due to leakage into the reservoir. Some years ago a small epidemic in a fraternity house in Ann Arbor was found to be due to specifically infected cistern water. One student already infected with typhoid fever, returning from his Christmas vacation, was ill in the house and his excretions undisinfected were thrown upon the ground near the cistern and were washed by subsequent rains into the reservoir. Other students in the house contracted the disease from drinking this water.

By surface water, we mean one which is collected above the first impervious geological formation, and this includes the waters of rivers, lakes, ponds, and shallow wells. All surface waters should be regarded as suspicious and should be subjected to frequent bacteriologic examination and to be perfectly safe should be filtered, chlorinated, or boiled. Village and city supplies should be filtered or chlorinated, or carried through both processes. It is not safe to rely upon the family to boil the water. In the selection of water-supplies for villages and cities, expert sanitary engineers should be chosen, and the care of the filtration and chlorination apparatus should be in the hands of competent persons. Bottled waters often show a large bacteriologic content, but we know of no instance in which typhoid fever has resulted from the drinking of such water, though this possibility is by no means excluded.

The disposal of human excreta is of prime importance in the eradication of this disease. In cities and villages water carriage is at present the only feasible method of disposing of this waste. However, to build sewers is not sufficient; ordinances must require sewer connections. The effluent from sewers must be rendered harmless before it is discharged into any stream or other body of water. Under the head of hookworm

disease we have discussed privy vaults and other methods for the disposal of human excreta in rural districts.

If antityphoid vaccination has proved so successful in protecting the American soldier against this disease, why should not the American civilian receive the same treatment? Certainly, the value of this form of vaccination should be explained to our high school, college, and university students, and they should be recommended to secure it. For some years this has been done in the University of California under the direction of Gay. Voluntary vaccination is now offered to students in certain other American universities. However, it is not likely that this form of protection will ever be so effective among civilians as it has been in military life. It will hardly be feasible to make it compulsory; it is not likely to be universally employed, and it will not be supported by the other safeguards against infection employed in camp and field. It has been used, and should be more generally employed, in institutions, hospitals, reformatories, prisons, asylums, etc. Indeed, some most striking results quite equal to those secured in military life have been obtained by institutional vaccination. Hatchel and Stoner vaccinated 5,512 individuals in state institutions in Maryland and found that by this procedure the morbidity was reduced to 58 per 100,000, while in previous years it had run from 500 to 2,000 per 100,000. Besredka reports that in a French asylum there were no cases of typhoid fever among 516 vaccinated individuals, while there were four cases among 434 unvaccinated. However, Wade and McDaniel report that in a Minnesota asylum, where carriers were subsequently shown to exist, there were a considerable number of cases among the vaccinated as well as among the unvaccinated, in spite of a positive Widal in the former, and they correctly suggest that vaccination alone is not sufficient to exterminate typhoid fever in institutions.

Bibliography

- BUDD, W.: Typhoid Fever; Its Mode of Spreading and Prevention, London, 1873.
 CHILDS, C.: A Study of the Typhoid Epidemics in the U. S. Volunteer Encampments in 1898, London, 1906.
 DUBLIN, L.: Am. Jour. Pub. Health, 1915, v, 20.
 GAY, F. P.: Typhoid Fever, New York, 1918, Macmillan Company. (This book contains a list of the literature up to the date of its publication.)
 GWYN, N.: Johns Hopkins Hosp. Bull., 1898, ix, 54.
 HAMILTON, A.: Jour. Am. Med. Assn., 1903, xl, 576.
 KLEBS, E.: Arch. f. exp. Path. u. Pharmacol., 1881, xiii, 381.
 KOBER, G. M.: Trans. Assn. Am. Phys., 1909.
 LOUIS, P. C. A.: Recherches anatomiques, pathologiques et thérapeutiques sur le maladie connue sous les noms de fièvre typhoïde, etc., J. B. Baillière, 1841.
 MURCHISON, C.: A Treatise on the Continued Fevers of Great Britain, Sec. Ed., 1884.
 OSLER, W.: The Problem of Typhoid Fever in the United States, Baltimore, 1899.
 PARK, W. H., AND WILLIAMS, A. W.: Pathogenic Microorganisms, New York, 1910, Lea & Febiger.

- REED, W., VAUGHAN, V. C., AND SHAKESPEARE, W. O.: Report on the Origin and Spread of Typhoid Fever in U. S. Military Camps during the Spanish War, 1898, Washington, 1904.
- RIST, E.: *Ann. de Méd.*, 1916, iii, 88.
- ROSENAU, M. J.: *Preventive Medicine and Hygiene*, New York, 1913, Appleton & Company.
- RUSSELL, F. F.: *Jour. Am. Med. Assn.*, 1913, lxi, 665.
- VAUGHAN, H. F., AND WALKER, W. F.: *Jour. Lab. & Clin. Med.*, 1915-1916, i, 371.
- VINCENT, H., AND MURATET, L.: *Fièvres typhoides et paratyphoides*, Paris, 1916.
- WHIPPLE, G. C.: *Typhoid Fever: Its Causation; Transmission and Prevention*, Wiley & Sons, 1908.
- ZINSSER, H.: *Infection and Resistance*, New York, 1914, Macmillan Company.

CHAPTER XII

ASIATIC CHOLERA

Definition.—This is an acute, highly fatal, intestinal disease, due to a specific bacillus, *B. cholerae*. Asiatic cholera is endemic in the Delta of the Ganges, from which locality it has from time to time, following lines of human travel, passed to the most remote parts of the earth.

History.—Macnamara is inclined to believe that a disease described under the name of *vishuka* by Susruta who lived six centuries B.C., was identical with what we now know as Asiatic cholera. Susruta describes this disease as marked by severe purging, vomiting, and consequent exhaustion, suppression of the voice, sunken eyes, coldness of the body, and a high fatality. Certainly, this description fits Asiatic cholera better than any other disease and Susruta, who lived in the region now included in the Northwestern Provinces, states that the disease was sporadic and recurrent. The first European to describe Asiatic cholera was Correa, a Portuguese, who states that during the year 1503, 20,000 men died in the Army of the Sovereign of Calicut, and that this high mortality was in part due to a disease which struck with so great pain in the abdomen that a man did not last for more than eight hours. The same author describes a similar epidemic at Goa in 1543, and states that so grievous was the throe that a violent poison was believed to be the cause. In 1563 d'Orta, another Portuguese, described an epidemic in Goa, known to the Arabs as *haiza*, which name is still used by Arabs in India to designate cholera. A Dutchman, Linschot, reported a highly fatal disease, characterized by severe purging and vomiting, in Goa in 1589. The first Englishman to describe cholera in India was Paisley, who wrote of an epidemic in Madras in 1774. Writing to an army officer, Paisley said:

“I am happy to hear you have occasioned the army to change its ground, for there can be no doubt, from the circumstances you have mentioned, that their situation contributed to the frequency and violence of the attacks of this dangerous disease, which, as you have observed, is true cholera morbus, the same they had at Trincomale.”

In 1781 an English line officer, Pearse, marching through the District of Ganjam with 5,000 Bengal troops, described his experience as follows:

“Death raged in the camp with horror not to be described, and all expected to be devoured by the pestilence. In vain I studied to discover the cause of our misfortune. I attributed it to a poison, but at length found that *there had been a*

pestilential disorder raging in the parts through which our first marches lay, and that part of our camp was already drinking the air of death and destruction.'"

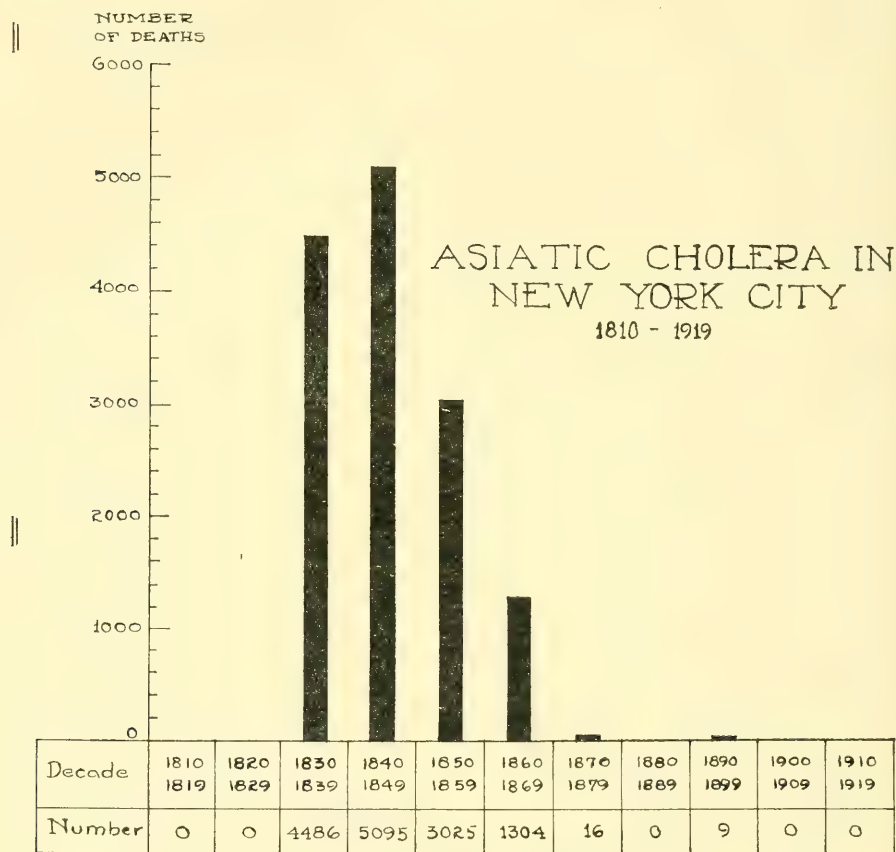
According to Macnamara, an epidemic broke out at Hurdwar in 1783 among pilgrims and is reported to have killed 20,000 within eight days. This author, after studying the history of cholera in India prior to 1816, came to the following conclusion:

"We are, therefore, I think, justified in arriving at the conclusion that it was nothing new for cholera to spread over India in an epidemic form prior to 1817 and 1819. The nature of the disease was then for the first time fully recognized, and as the greater portion of the country had passed under our rule, British officers were in a position to trace the progress of the disease over the length and breadth of the land."

In 1816 this infection began its first recorded travels and reached countries so remote that it could be regarded as pandemic. The time assigned by Haeser to the first great excursion of this infection extended through seven years (1816-1823). It traveled slowly at that time, before the general use of steam transportation, and did not get beyond the confines of Asia and Africa. To the east and south it visited Borneo, Java, the Philippines, and China. To the west and north it spread through Arabia, Persia, Syria, Egypt, and northern Africa. It lingered in various localities some years, after which it was known only in its home until 1826 when the second visitation began. This continued for 11 years, terminating, according to Hirsch, in 1837. This time it spread over the greater part of Europe and America. It broke up into parties which traveled different routes, some by sea and some by land. The faithful from Farther India brought it to Mecca where it found ready but slow transportation to all points of the compass. Nothing more was known of the infection outside its own domicile until 1846. The third pandemic reached the farthestmost parts of the earth and lasted until 1862. It killed in France alone, in 1853-1854, nearly 150,000 and it pursued the gold seeker on his way across the plains to California. The fourth pandemic was well in evidence by 1864 and continued until 1875. As the records show, it found 114,683 victims in Prussia alone on this trip. The fifth pandemic began in 1883, spread over the Eastern Hemisphere and reached New York Harbor, but was refused admission. This time the number of victims in European Russia alone is given at 800,000. The notable outburst at Hamburg belongs to this period. In 1902 cholera for the sixth time became pandemic. It was disseminated by 400,000 pilgrims gathered together at Mecca. Since that time and up to the present it has been found in various parts of Europe and has repeatedly reached our own shores, but has not been permitted to gain a foothold.

In all these excursions, among all kinds and conditions of men, in

every degree of civilization, in the tropics and amid the snow and ice of northern Russia, in the thronged city and in the emigrant's wagon, with high and low, slave and master, wherever it has traveled, cholera has maintained its individuality and has shown no modification in manner of attack or variation in the symptoms induced in its victims. Its vehicle of transport has been man's body and it has followed the lines of



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Fig. 28.

human travel, on foot, on horse or camel, by stage or ox team, by steam on land and sea. The sick and dying have scattered its progeny around the world. The science of preventive medicine is the only detective who can trace this criminal, the only officer who can arrest it and the only executioner who may finally remove it for all time from the earth.

The studies made of the cholera pandemics from 1817 to 1870 greatly advanced the science of epidemiology. The progress of no other epi-

demic disease has been traced with the accuracy secured in these studies. The exact pathways from Mecca and Hurdwar through Asia, Africa, and Europe, across the Atlantic, and to the Coasts of the Pacific, traveled by certain epidemics, were accurately determined, with time required for successive advances and for occasional detentions. The study of these epidemics did more than anything else to show the falsity of miasmatic and constitutional theories. During the period mentioned, many papers were written on the epidemiology of Asiatic cholera. Among these is, "A Treatise on Asiatic Cholera," by Macnamara, published in 1870. This book deserves to be a classic in the annals of epidemiology, although, so far as we can judge, it has been but little read. Taking this book as a summary of the knowledge gained concerning the epidemiology of cholera before the discovery of the bacillus, we here-with condense certain statements and facts, amplifying some of them with quotations from the book:

(1) Asiatic cholera is a specific disease.

"Cholera is a disease which is generated at all seasons of the year, among human beings inhabiting certain parts of India; it is capable of being disseminated over the world through the instrumentality of the fomes of those who have suffered from the disease, though it may be only in a mild form, usually described as cholerine. * * * I need hardly say this (Asiatic cholera) differs essentially from sporadic cholera, which no one ever supposed to be communicable, either in this country or in any other parts of the world; and which evidently arises quite independently of any preexisting disease, usually from overindulgence in food, or from eating unripe fruits, or such like unwholesome matters. I am quite prepared to admit that there is an analogy between the diseases; I believe they are both connected with changes in the epithelial lining of the intestinal canal, but in the sporadic form, there is no evidence to show that the fomes are capable of setting up a special and deadly molecular action in the intestines of otherwise healthy people, which is characteristic of Asiatic cholera, giving rise to the rice-water alkaline stools, and the rapid death which too frequently follows this form of disease."

(2) Up to the time of the British occupation of India, cholera was known only in that country. This does not mean that in more remote times it may not have been transported to other countries, but if so, it had died out in the lands to which it had been carried and in the beginning of the nineteenth century it existed in India only.

"A characteristic feature of epidemic cholera is, that every outbreak of the disease beyond the confines of British India may be traced back to Hindustan, through a continuous chain of human beings affected with the disease, or through articles stained with their dejecta. In other words, the train of phenomena resulting in cholera beyond the confines of India must have commenced in this country; consequently, America, Europe, and the greater part of Asia may justly blame India for all they have suffered from cholera. * * * Cholera has in this course invariably followed the routes by which man travels, and if it has thus spread from country to country by his agency, then we may fairly assume that it has extended continuously from man to man."

(3) Cholera never originates *de novo*.

"The fourth characteristic of cholera I have to notice is, that no amount of overcrowding, no special condition of the soil, nor any circumstance with which we are acquainted, has ever been known to originate Asiatic cholera *de novo* among men removed from its endemic influence, or unless the disease has been epidemic at the time beyond the confines of India."

(4) The spread of cholera from place to place and from country to country has depended upon human intercourse between infected and uninfected areas.

"And here, again, let me draw the reader's attention to the facts, that Australia and other large tracts of country have as yet been free from the disease, and that these places are separated from India by extensive oceans or seas; on the other hand, that as our communications with Europe have become more constant and rapid, so has epidemic cholera become more frequent in its visits to that continent, invariably pursuing the route followed by man in his passage to and from India, halting for a time in intermediate countries, where the seeds of the disease have been sown to bear fruit in due season, whence fresh germs have been again transmitted to other men, who have carried it a step farther towards the west. Thus has the malady been propagated from one human being to another, until its influence has spread from the east as far as the western shores of America. But cholera has never appeared in America unless Europe has been first affected; it has never broken out in the west of Europe unless the eastern part of the continent has been previously under its influence; and it has never been generated in the east of Europe unless correlated with an outburst of the disease in Turkey-in-Asia, Arabia, or Persia; nor have these countries been affected until the disease had previously burst out with violence over Bengal and traveled by slow and steady steps to the west of India."

(5) The direction of the spread of epidemic cholera has been determined by the paths of human travel. In 1865 cholera broke out among the pilgrims in Mecca. It is supposed that of 90,000 there assembled, more than 30,000 fell victims to this disease. The 60,000, more or less, of those affected fled towards their homes. Thousands of them took passage on the Red Sea at Jeddah and in May of that year arrived at Suez and were transferred to Alexandria, where the epidemic spread among the natives. From Alexandria the disease was carried by ship to Constantinople, thence around both the southern and northern shores of the Black Sea to Trebizond, Erzerum, and other places; also to Odessa. From southern Russia it was transported into Germany, where it became epidemic in many localities. Other ships carried infected persons from Alexandria to Italian, French, and Spanish ports. The epidemic records of that time permit one to make an exact map showing the distribution of the disease, and in most instances we are able to name the ship on which epidemic cholera traveled. Even before the Christian era it had been observed that epidemic diseases usually traveled from east to west. A study of cholera epidemics shows that this disease traveled

east, west, north, or south, or to any point of the compass to which infected persons might turn their faces and direct their steps.

(6) Places along routes of epidemic travel to which infected individuals were not admitted remained free from the disease. Land quarantine was not easily rendered effective. In 1831 great effort was made to keep the disease out of Russia. This failed, because rivers, both large and small, became infected; ultimately, other water-supplies also received the infection, and the disease traveled throughout the length and breadth of the country. A supreme effort was made to keep the disease out of St. Petersburg, but this also failed, and the canals and river courses with which that city is traversed became grossly polluted. Finally the Court, with 10,000 attendants, repaired to Peterhoff, which was surrounded with an armed guard and no case of cholera occurred among those thus protected. When cholera appeared at Montreal the soldiers were removed from the city and stationed on a small island in the river, St. Helena. Here they remained and no case of cholera appeared among them. During the first two European epidemics Greece was able to isolate herself from the rest of the world and remained absolutely free from cholera. In 1854 that country, being at the time occupied by a foreign force, was no longer able to control quarantine; consequently, the disease found its way in and spread over the whole country. In 1865 Greece again protected herself against this disease.

(7) Cholera is not transmitted through the air by the ordinary intermingling of people.

"Cholera is not transmitted from man to man by contact, but by an organic infecting matter, passed with the evacuations of those affected, which must gain access to the intestinal canal of another person before he can be attacked with cholera. In this lies the whole secret of an effectual preventive treatment, for evidently, if we can destroy organic infecting matter the instant it has passed from the patient, cholera cannot spread; or, what amounts to the same thing, if we can prevent the infecting matter of the cholera dejecta from reaching the intestines of other persons, we prevent them from getting cholera. Our efforts in this direction will constitute the most truly scientific preventive treatment of this fearful disease. I appeal with confidence to the history of cholera for confirmation of the fact, that the disease has never yet appeared beyond its endemic area unless imported there from India by man. Every outbreak of it in Europe has clearly commenced in Lower Bengal and been carried directly by human agency to the four points of the compass, south with coolies to the Mauritius, eastward to the Straits and China, northward over the Himalayas, and westward right away to Europe and America."

(8) Cholera may appear simultaneously or nearly so at widely distant points and still come from the same place. In 1848 cholera appeared practically at the same time in New York and New Orleans. There was no possible way by which it could have been carried from one of these places to the other within the time, and this enabled people to say, as

they had been saying for centuries and some continue to say, that an epidemic is due to some terrestrial influence,—something which vitiates the air all around the world at the same time. Fortunately, it turned out that the simultaneous appearance of cholera in New York and New Orleans could be easily explained. In October and early November of 1848 German emigrants from a cholera infected district assembled at Havre. There was no cholera at Havre at that time. On the ninth of November the *New York* sailed for the city of that name with 315 of these steerage passengers. She was preceded by the *Swanton*, which sailed from Havre for New Orleans on the third of November with another batch of these infected emigrants. Cases developed on both ships when they were 1,000 miles apart, and in this way practically on the same day cholera cases appeared in New York and New Orleans. In the latter city the disease became epidemic and was carried up the Mississippi, Ohio, and Missouri Rivers so far as they were navigable; and in the spring of 1849 the seeds of this disease found transportation in the wagons of the gold seekers and its ravages followed the miner into the most remote camps.

(9) Cholera establishes itself and prolongs its stay in communities the drinking water of which becomes the bearer of the infection. One of the first to recognize this was Snow, who brought forward the evidence against the "Broad Street Pump," a case which has become a classic in the history of epidemiology. The excretions of a child sick with and finally dying from cholera were poured into a drain within a few feet of this well. Investigation showed that the bricks of this cess-pool were loose and that its contents flowed directly into the well. Within a few days cholera appeared among the neighbors. One day there were 143, another 168, new cases, and within 12 days the local epidemic had entirely ceased. To make the evidence against the well still stronger, a woman, who lived at Hampstead and who suffered from the delusion that no drinking water in all England could equal that which came from the Broad Street pump, had a bottle of this fluid brought to her residence every day. She and a servant who partook of the Broad Street water developed cholera, while there was no other case in the neighborhood. It is interesting to note that the College of Physicians investigated the claim of Snow that the disease was transmitted through the water, and while it admitted there was much to justify Snow's belief, it was most likely that the cholera poison was carried from place to place by the wind. The truth of Snow's demonstration that cholera is a water-borne disease finally secured full recognition, and it was this that led to the passage of the Metropolitan Water-Supply Act and to the sand filtration of water-supplies. By the time the International Sanitary Conference assembled at Constantinople in 1866 it

was generally agreed that Asiatic cholera is, for the most part at least, a water-borne disease; indeed, this Conference affirmed that cholera is never known to extend from place to place faster than man can travel; that it never lingers in a locality unless the water-supply becomes contaminated; that it never appears on board ship except when the ship leaves with infected persons or infected water.

(10) Even in sparsely settled districts cholera is introduced and spread by the coming of infected individuals.

“In the early part of 1852, extensive works of irrigation were in progress at the foot of the mountains in Kumaon (a district in the Northwestern Provinces). Several thousand workmen were collected there from the neighboring hills. Cholera broke out among these people with great virulence, and they fled panic stricken to their homes, which were generally at a distance of several days’ journey in the interior of the hills. Up to this time, cholera had been unheard of in Gurwhal, or in any of the neighboring mountains. This is a fact that was carefully inquired into and thoroughly ascertained. Many of the work-people who fled from Kumaon died on the way to their homes; many others were attacked when they reached their villages. There, cholera broke out among the other inhabitants of the villages, commencing, in very many instances, in the families of the men who had brought the disease from below. For a considerable time cholera was entirely confined to places which had been in direct communication with persons suffering from the disease; but in the course of a few weeks it had become impossible any longer to trace such connection, and cholera became generally epidemic through the hills.”

(11) In all attacks on board ship it could be shown that the ship left port bearing the infection. In this way cholera during the Crimean War was transported from France to the Crimea on board French men-of-war. On certain of the ships only distilled water was used and on these there was no cholera. On ships on which the drink was not confined to distilled water the disease was much more prevalent among the men than among the officers, and it is interesting to observe that this difference was attributed, partly at least, to the fact that the officers drank wine, tea, and coffee, while the men had water straight or diluted their grog with infected water.

(12) When water is taken from a tidal river a city may suffer from its own sewage, even though the water intake is above the city. This was the experience at Newcastle in 1853. The conditions existing at Newcastle at that time were fully investigated and thoroughly understood. At that time Newcastle took its drinking-water supply from the Tyne at Elswick. The sewage of the city was carried by the tide up the river and polluted the water-supply. This experience was practically repeated, with most serious results, at Hamburg nearly 40 years later.

(13) When a city water-supply becomes infected with the cholera virus there is a sudden outburst of the epidemic, which soon reaches its maximum and then declines. The truth of this was made evident in the

experiences of many cities. In 1831 on the third day after the first case was recognized in Paris, patients were received at the Hotel Dieu from every part of the city and numbered many thousand. It was well recognized as long ago as 1831 that water contaminated with the cholera virus induces the disease for a few days and then loses its infectious quality.

“This theory, moreover, includes what I am convinced of as a fact, that epidemic cholera has invariably sprung from a preexisting source of disease; that it is impossible for it to break out in a locality beyond its endemic area, unless the organic matter from another person suffering from cholera has been introduced into the place through the agency of man; and that, as the vibronic decomposition cannot be set up in organic matter, unless with the aid of moisture and a certain temperature, so cholera depends greatly for its diffusion upon drinking water and the range of the thermometer. Lastly, this contaminated water must be swallowed during a particular stage of the decomposition of the organic matter in order to produce any ill effects, for as oxidation goes on the water purifies itself, and in the course of a few days becomes innocuous.”

(14) The cholera virus grows and multiplies in the intestine of man and leads to necrosis of the epithelium, resulting in the exudation of large quantities of blood serum and the discharge of rice-water stools. Physicians of the time of which we are now writing made accurate and thorough postmortem examinations and, indeed, established the fact that in Asiatic cholera the most characteristic anatomic lesion consists in the destruction of the intestinal epithelial cells.

(15) Long before the discovery of the cholera bacillus, experts in the study of this disease knew quite well that the cholera virus is highly susceptible to acids and they emphasized the fact that the normal acidity of the gastric juice plays an important rôle in individual protection against this infection; indeed, a popular method of treatment at that time consisted in the administration of dilute sulphuric acid continued until acid stools became evident.

(16) As early as 1848 Budd, of Bristol, England, not only supported Snow in his claim that cholera is largely distributed by drinking water, but recommended that cholera stools should always be disinfected. He made successful demonstration of this recommendation when in 1865 he had opportunity to treat an outbreak of cholera at Bristol. The disinfectant which he used for cholera stools is the sulphate of iron recommended on account of its acidity.

(17) It was well understood by English physicians that in endemic localities in India the drinking water was repeatedly, and we might say constantly, polluted specifically by the natives.

“It may not be commonly known in Europe, that a native of this country, after an attack of cholera, will, as a general rule, crawl down to the nearest tank, and with the cotton cloth around his body—which, in all probability, he has had on during his illness—he wades into the tank up to his middle; he afterwards divests

himself of his cotton garment, which he proceeds to wring out. Having washed it, he again coils it round his loins, and walks out of the water. Very probably, at the time this process is going on, a man or woman may be seen not far off filling an earthen pot, or a mussuckful of water, which is carried away and employed for drinking and other domestic purposes. River water may be contaminated in precisely the same way. Lastly, supposing the cholera patient dies; if a poor man, his friends cannot afford fuel to burn the body; it is, therefore, for form's sake, just singed with fire, and then thrown into the nearest river, to contaminate its water for days as it floats down stream."

(18) Drinking water in any part of the world infected with the cholera virus may cause the disease. It was clearly understood by these early students of cholera that no amount of pollution in drinking water, so long as the specific virus was not present, could cause Asiatic cholera; on the other hand, it was equally well understood that no drinking water, however pure it might be naturally, could fail to be specifically contaminated on the addition of cholera stools and become the bearer of the disease.

(19) The fact that cholera is usually disseminated by infected drinking water does not exclude the possibility of infection being brought about otherwise. It was frequently observed that laundry women became infected by handling specifically soiled garments and bed linen; indeed, Macnamara and other cholera experts of that time believed that dried cholera stools retained their infectious properties indefinitely.

(20) It would be relatively easy to arrest the progress of cholera epidemics, especially those traveling by sea, by moderate detention, examination, and disinfection. The International Sanitary Congress held in Constantinople in 1866 provided for quarantine stations which have continued to develop in efficiency, with occasional lapses, up to the present time.

We have gone into some detail concerning the facts learned about the epidemiology of Asiatic cholera before Koch identified the bacillus of this disease. We have done this for two reasons. In the first place, we wish to emphasize the fact that it is not absolutely necessary to be able to identify the specific virus of a disease in order to possess oneself of important truths and practical measures in its control. In the second place, as we have already hinted, a study of cholera epidemics has given new viewpoints for the study of other epidemic diseases; in other words, our increased knowledge of the epidemiology of cholera has given us basic facts in the study of epidemics due to other diseases.

The Bacillus.—In 1883 the German Government sent a commission with the distinguished bacteriologist, Robert Koch, at its head, first to Egypt and then to India to ascertain the cause of this disease. Many months were spent in the study of the discharges of the sick, the post-mortem examination of the dead and the investigation of the food and

drinking water of the infected. The result was the discovery of the infective agent, and this has placed in man's hands the possibility of completely eradicating this disease. The bacillus is a slightly curved rod, averaging about 1.5 microns in length and one-third this in breadth, but with many variations. Frequently, many individuals are attached, end to end, forming something like the letter "S." It is known as the comma bacillus or the cholera vibrio. It is distinguished from similar vibrios by having a single flagellum or whip at one end. Its rapid motility in suspension is due to this whip. Sometimes the form is ovoid, often much longer and shows a long whip. It is easily recognized in the stools by an expert and the diagnosis in suspected cases is easy and certain. It takes the ordinary basic stains easily and deeply, but in order to stain the whip a mordant dye is desirable. It grows rapidly on gelatin plates at 22° C. (71.6° F.), forming within 24 hours, colonies visible as small bright points.

Under a low power the colonies appear like fine bits of glass strewn over the gelatin. They are easily distinguished from colonies of *Bacterium coli*, found in normal stools, by their greater refraction. After 48 hours the gelatin under and about the colony begins to liquefy, forming a small funnel or crater in the bottom of which lies the colony. Old subcultures develop colonies on gelatin plates which are less characteristic than those freshly obtained from cholera stools. In gelatine stick cultures the bacillus grows along the line and looks like a white thread. Liquefaction begins at the top and extends downward forming a funnel-shaped depression. Colonies grown on agar plates are also quite characteristic. On other media it grows quickly, especially so in alkaline one per cent pepton solution. The cholera bacillus does not grow in the absence of air and consequently is known as an obligate aerobe.

The cholera bacillus grows most abundantly at or a few degrees above body temperature and does not wholly cease to multiply until the temperature is at or below 8° C. (46.4° F.). Freezing does not destroy it and it retains its virulence after having been frozen in ice for several days. It is quickly destroyed by drying. A drop of bouillon culture placed on glass and allowed to dry in the diffuse light of a room shows no growth when placed in proper medium after two hours. When exposed to direct sunlight, life is destroyed in even less time. This indicates that the bacillus does not form spores and that the disease is not air borne.

Boiling destroys the bacillus instantly; at 80° C. (176° F.) five minutes is long enough to destroy its vitality and a temperature as low as 55° C. (131° F.) has the same effect after half an hour. It is also highly susceptible to chemical agents. One per cent carbolic acid, 1:3,000,000

corrosive sublimate and feebly acid solutions kill it within a few minutes. According to Harding, one part of chlorin to one million parts of water destroys the bacillus within 15 minutes. In distilled water it soon dies but in ordinary drinking water or tank water, such as is used in India, it may retain its vitality and virulence for weeks and even months. According to Hankin, the organism soon dies in the water of the Ganges, which is feebly acid. How quickly it dies in stools depends on many conditions, such as dampness and light.

No lower animal, however intimate the contact with infected men may be, is known to develop cholera. This disease seems to be, at least under natural conditions, confined exclusively to the human species. Furthermore, no one has succeeded in inducing a true cholera in an animal by inoculation. However, some of the attempts to accomplish this purpose have been partially successful and are of sufficient interest to justify brief review. Filter paper impregnated with cholera cultures or stools fed to mice induces diarrhea, but filter paper alone has the same effect. This was demonstrated by Burdon-Sanderson years before the discovery of the bacillus. Large quantities of cholera cultures fed to pigs cause death, but cultures of many other bacteria produce like results.

Before 1870 Macnamara had attempted to infect the lower animals with cholera stools. He opened the abdominal cavities of dogs and injected rice-water stools directly into the small intestine, without result.

Nikati and Rietsch opened the abdominal cavities of guinea pigs, tied the bile duct in order to exclude the bactericidal action of this fluid, and injected cholera cultures into the duodenum. In the intestines of the recovered animals the cholera bacilli multiplied and the epithelial lining of the intestines was found altered. Other bacteria behave in a similar manner. Koch neutralized the stomach contents with soda and then introduced cholera culture into this organ through a tube. At the same time the animals were stupefied with opium from which they soon recovered, but the next day became ill and died on the second or third day in collapse. After death the intestine was found to contain a colorless fluid consisting of a pure culture of the comma bacillus. Like results may be secured with other vibrios; indeed, Metchnikoff did better in his experiments on rabbits with the *Vibrio Maszauah* which is known to be quite different from Koch's comma bacillus. He polluted the teats of a mother rabbit with this culture and found that at least half of the nursing young died of a choleraic diarrhea. Moreover, when the sick young rabbits were placed in a cage with healthy fellows from another litter, many of the latter became infected. Thomas injected cholera cultures into the ear veins of rabbits. After a few days the animals died and inflammatory changes were found in the walls of the intestines and cholera bacilli in the intestinal content.

Many bacteria when injected intravenously find their way into the intestine and may induce the same changes in the intestinal walls. Cholera cultures injected into the abdominal cavities of guinea pigs cause a fatal peritonitis. Many saprophytic organisms will act in the same way and quite as promptly. It is safe to say that all attempts to induce genuine and distinctive Asiatic cholera in the lower animals, made up to the present time, have failed, and that we know no animal susceptible to this disease under either natural or experimental conditions. To man alone belongs the function of serving as host, preserver, and distributor of the comma bacillus. Without man to supply warmth, shelter, food and transportation, the cholera bacillus would soon disappear from the face of the earth.

Every man who goes into battle is not killed; likewise not every man who swallows the cholera bacillus becomes infected and of the infected all do not die. The cholera bacillus is highly susceptible to acids, and the acidity of the stomach is a protective agency. But the acidity of the stomach is widely variable among people and scarcely less so in the individual from time to time. Infected drink, taken when the stomach is empty and nonacid, is likely to carry its infection on into the alkaline intestinal content. Bacilli protected by masses of food, difficult of digestion, may also pass through. In the midst of cholera epidemics, many harbor the bacillus and distribute it in their stools without being at all affected by it. Others are only slightly ill and there is every degree of gravity up to those in which the disease is fatal within a few hours.

In typical cases of cholera the bacillus does not find its way through the intestinal walls. It multiplies so abundantly in the intestinal content that it starves out all other bacteria and after death there is a pure culture in the intestine. It not only grows abundantly, but its cells speedily die and in doing so the poison contained in their structure is liberated, exerts its local effects on the intestinal walls, is absorbed and produces the symptoms of the disease, and death. In fact, cholera as an infection is limited to the alimentary canal; as an intoxication it kills. There seem to be exceptional cases in which there is a general infection, Rabowski having reported the finding of the bacilli in the liver, kidney, and heart.

In acute cholera the bacillus is found only in the intestine and gall bladder after death. All other organs and tissues are sterile. The intestine is converted into a great culture flask from which the chemical poison, elaborated by the bacterial growth, diffuses into the blood, while the water from the blood diffuses into the flask. This results in the condensation of the circulating blood, the drying out of the tissues, the suppression of urine, perspiration, saliva, and even of tears. The chol-

era poison, irritating the intestinal wall, increases peristalsis until it becomes most painful and leads to the ejection of large volumes of rice-water stools. The constant nausea and vomiting render even drinking quite impossible. Through mouth and anus the culture flask is discharged while it is constantly replenished by the withdrawal of water from the blood and tissue. In the acute form, a few hours suffice to dry out the tissues so thoroughly that death results.

Several cases of laboratory infection with the cholera bacillus have been reported. The first of these occurred in Koch's laboratory in 1884. A careless worker infected himself. Dr. Oergel, of Hamburg, died from accidental infection with the cholera bacillus. Some half-dozen additional laboratory infections have been reported. Besides these accidental infections, several have intentionally swallowed cultures. The most notable instance of this kind was that of the Munich professors, Pettenkoffer and Emerich. They alkalized their stomachs and then drank the dilute cultures. The former suffered only a severe diarrhea, but the other passed into the algid stage with suppression of urine and barely escaped with his life. A similar instance occurred in Paris under the observation of Metchnikoff. It has been observed in these cases that the period of incubation is short, from 24 to 48 hours.

The cholera poison, on which much work, ending in diverse and even contradictory conclusions, has been done, is probably the protein poison found in all proteins. Ordinarily this poison is without effect when given by mouth on account of the slowness with which it passes the intestinal wall, but with the lumen of the intestine filled with an abundant cholera culture, the walls are so injured that the poison is rapidly absorbed. The cholera poison is not more active than that obtainable from other bacteria, both pathogenic and nonpathogenic; also from other proteins both vegetable and animal.

Sources of Infection.—Every case of cholera means that some one has swallowed bacilli which have come from the stools of some one else. The route may have been quite short and direct or may have been long and circuitous. The bacilli bred in the intestine of one individual may find their way into the mouth of another, or many generations of bacilli may lie between the two subjects. In all instances, the connection is sure and certain. This disease spreads in no other way. The only infected discharges from the cholera patient are those that come from the alimentary canal. The vomited matter may contain virulent bacilli but this is rarely the case, on account of the great susceptibility of the organism to acid solutions. Practically the only infectious discharge is the stool. Among filthy people the stool may go quite directly to the mouth by the hands. Mothers often infect their children in this way and sometimes it is transferred from child to parent.

This contact infection is illustrated in the voyage of the *Carlo R.* which sailed from Naples, August 1, 1893, for Brazil, with 1,472 steerage passengers. The ship's water was not infected. On the outward trip cholera appeared. On reaching South America the vessel was not permitted to dock and was compelled to return. The double voyage occupied two months and during this time there were 141 deaths among the steerage passengers. Scarcely less direct is the transference from soiled clothing or bedding or when the infected stools are deposited on fruits and plants which are subsequently eaten. The less cleanly people are, the more liable they are to acquire this disease.

Before the discovery of the bacillus, Pettenkoffer had observed that, in its European visitations, this infection spared certain localities. These were relatively clean places, such as would not afford opportunity for contact infection. The great outbreaks, such as that at Hamburg in 1892, are due to infection of the general water-supply. At that time Hamburg used the unfiltered water from the Elbe. At first there were a few cases among those employed about the wharves. Finally the pollution extended up the river and reached the city water-supply. The first case was recognized early in August and the explosion came on the twentieth of the same month and by the thirty-first the number of new cases per day reached 1,000. Hamburg and Altona are one city, but separated administratively. On one side of the street the houses are in Hamburg and on the other in Altona. The latter had a separate and uninfected water-supply and was free from the disease except among those who drank from the Hamburg water.

Certain cities in Italy, notably Naples and Genoa, have in recent years been mildly infected and the disease has been kept alive by contact infection, but their water-supplies being free from pollution, severe outbreaks have not developed. Suspected persons and their families and neighbors should be tested by an examination of their stools and kept under observation so long as these contain the bacilli. A convalescent may carry the organism in his intestine and expel it in his feces for 60 days after recovery. Many who do not develop the disease carry the bacilli and distribute them in their stools.

Vaccination.—During the prevalence of cholera in Spain in 1885. Ferran attempted to prevent the spread of the disease by subcutaneous injection of cultures obtained from stools and from the intestines of those dying of the disease. We wish that we could claim for this village doctor in Spain a high degree of scientific merit and the possession of knowledge far in advance of his time, but, after reviewing the voluminous literature concerning his work, we are compelled to conclude that he was an empiric and apparently more largely concerned with the notoriety brought to him than with the scientific aspects of the case. How-

ever, we must give him the credit of being the first to attempt to vaccinate against Asiatic cholera. Although his results were not scientifically assembled it seemed to be the impression of the various scientific commissions who investigated his work that his treatment actually was of value in the prevention of the disease.

In 1893 Haffkine, after a most elaborate series of experiments upon laboratory animals, in which he was undoubtedly influenced by the success of Pasteur in the preparation of anthrax and rabies vaccines, prepared cholera vaccines of definite strength. He selected highly virulent cultures of the vibrio and intensified these so far as possible by successive intraperitoneal injections in rabbits or guinea pigs. These organisms are grown on agar and washed off with sterile broth, 8 c.c. of which constitutes a dose and which is injected hypodermically in the groin. In rabbits and guinea pigs this preparation causes a severe local reaction which may lead to extensive ulceration and sloughing. Seeing this decided effect upon the lower animals, Haffkine concluded that this form of vaccine could not be used in man and he prepared a second vaccine by growing vibrios at a temperature of 39° C. He found experimentally that when the milder vaccine was employed and some days permitted to elapse, the stronger virus could be used without inducing an unpleasant reaction. For a while, therefore, he used in a routine way these two vaccines. Later he found that the stronger preparation could be used in man without marked inconvenience. Consequently, he dropped the second vaccine and for more than 25 years Haffkine's preparation has been used in India. Statistics show that this vaccine reduces liability to the disease to about one-tenth and increases the chance of recovery among those who do acquire the infection. Several hundred thousand people in India have been subjected to Haffkine's vaccine. Powell states that among 6,549 unvaccinated there were 198 cases with 124 deaths, while among 5,778 vaccinated, similarly exposed, there were 27 cases with 14 deaths. It is believed that the protective effect of the vaccine lasts for about one year only, when revaccination is desirable.

At the time of the cholera epidemic in Manila in 1905, Strong prepared a cholera vaccine which consisted of the filtrates obtained by passing cultures through a Berkefeld candle. Filtrates were obtained from living cultures and from those which had been heated for one hour at 60° C., these filtrates being mixed in equal proportion. This prophylactic is preserved in 0.5 per cent carbolic acid and is transported in sealed glass tubes. Two c.c. constitutes a dose. So far as we know, Strong's preparation has not been used on a large number of people. At the present time Haffkine's vaccine, consisting either of the living organisms or of sterile cultures, is the one generally employed. During the World War, cholera vaccine was largely employed in the armies on

both sides. So far as we know, cholera prevailed more or less in the armies of Russia, Serbia, and Austria. From a German source we learn that from May 23, 1915, to January 15, 1916, there were 22,128 cases of cholera with 11,787 deaths, in the Austrian Army. It appears that up to the time of the first-mentioned date, vaccination had not been practiced. We have not been able to find any official figures concerning the prevalence of cholera in other armies or in the Austrian Army at other times. Hoffmann states that cholera vaccination was completed in the German Army by the end of November 1914, and that it was successful not only among soldiers, but in the civil population as well. The same authority is responsible for the statement that this disease was introduced into Germany by Russian prisoners and that sporadic cases did occur among civilians, especially in the eastern part of the German Empire. It is reported that an epidemic of cholera appeared in Warsaw in August, 1914. Furthermore, we have evidence that this disease in the first year of the war played quite an important part in the high mortality among Serbian soldiers.

In 1909 Castellani prepared a tetravaccine for typhoid, paratyphoid A, paratyphoid B, and Asiatic cholera, which was introduced into the Serbian Army in 1915 with apparently good results. Castellani gives the following method of preparing the vaccine:

“The growth of typhoid cultures (on agar) is washed off with sterile 0.85 per cent solution, to which 0.5 per cent carbolic acid has been added; the emulsion so obtained is stored at room temperature (18° to 20° C.) for 24 hours, and then standardized. To standardize it the germs are counted by using a Thoma-Zeiss apparatus, and sufficient carbolic salt solution is added to bring the number of germs down to 2,000 millions per c.c.

The standardized emulsion is tested for sterility. The same procedure is carried out with paratyphoid A and paratyphoid B cultures, these two emulsions being also standardized to contain 1,000 million germs per c.c. The above procedure is also carried out with cholera, the emulsion of which, however, is standardized to contain 4,000 million germs per c.c. The four standardized emulsions when found sterile are mixed together in equal proportions, and the vaccine will therefore contain per c.c.:

Typhoid	500 millions
Paratyphoid A	250 millions
Paratyphoid B	250 millions
Cholera	2,000 millions

Of this mixture, 0.5 to 0.6 c.c. are given under the skin of the arm, or better into the loose tissue below the angle of the scapula, the first time, and double the amount a week later. A third dose, also $\frac{1}{2}$ c.c., given two weeks after the first, is of advantage, but not essential for practical purposes. The amount of agglutinins for each germ is about the same as if a monovalent vaccine had been injected. The protection for cholera seems to last for about six months.”

It is an interesting question how vaccination can prove of value in cholera, since bacteria are confined, even in fatal cases, to the intes-

tinal canal. Up to the present time this question can be answered only theoretically. It is known that, while the vibrios do not pass through the intestinal walls, they do penetrate the epithelial tissue of these structures, and that their presence in these localities causes the blood serum to flow into the lumen of the intestine; therefore, it is reasonable to suppose that the blood serum, containing bactericidal substance, destroys the cholera vibrios in the epithelial layers and possibly may have some destructive action upon those organisms remaining in the lumen of the intestine. Strong undertook the task of determining whether the rice-water stools of cholera have any specific bactericidal action upon the vibrios. However, he found this a complicated task and was unable to arrive at any satisfactory conclusion. It seems quite certain that the only way in which a vaccine introduced subcutaneously might protect against such a disease as cholera is by the production of bactericidal substances. Cholera is probably the most striking example among all diseases of the action of the protein poison. As was shown by the work of Pfeiffer many years ago, cholera cells are easily broken down with the liberation of a soluble poison; in fact, this experiment gave Pfeiffer his ideas and concepts of endotoxins. The most reasonable explanation is that the cholera bacteria are broken down in the small intestine, either in the lumen or in the epithelial tissue, with the liberation of the protein poison which is absorbed and causes the symptoms and death. For the protein poison there is no antibody. It follows, therefore, that no antitoxin has ever been found for the treatment of this disease, and it is not at all likely that any such body will ever be found. As has been demonstrated by laboratory experiments, minute doses of the protein poison elevate the temperature, while large doses depress. As was shown by Chevers many years ago, Asiatic cholera is a febrile disease, notwithstanding the fact that the temperature in the axilla and in the mouth is generally below the normal and in the algid stage it may fall as low as 34° C. This is exactly what the protein poison does when thrown into the body in lethal doses. In another respect cholera resembles protein poisoning. The rhythm and force of the heart beats are but slightly disturbed. The pulse, even in the last hours, generally runs from 80 to 100, seldom reaching 120, and in practically all instances varies but little in its normal rhythm. Now we can understand how vaccination may increase the resistance to infection with the vibrio of cholera; that when this organism reaches the intestine in small numbers the epithelial cells of the intestinal walls may pour out a bactericidal substance which kills the invading organisms before they have time to multiply sufficiently to furnish a lethal dose when they are disrupted. Whatever the explanation, vaccination against Asiatic cholera has ap-

parently demonstrated its value and shown itself as an important adjunct to sanitation in the prevention of this disease.

Recognition.—During the prevalence of this disease, diagnosis of individual cases is easy. The sudden collapse, the rice-water stools, the vomiting, the algid stage, and the high fatality, can leave no room for doubt. It is when unsuspected that cholera may escape detection. In such instances a microscopic examination of the stools is generally sufficient. It is true that there are other vibrios which closely resemble that of Asiatic cholera, but when a smear made from a characteristic stool shows this organism, at least a tentative diagnosis is justified. As a rule, it is sufficient to make a smear from the rice-water stool and examine it, properly stained, under the microscope. This is sufficient in the great majority of instances for a preliminary diagnosis. Of course, in cases of doubt it should be followed up by further investigations. A bit of stool placed in pepton water and kept in the incubator for 24 hours shows a pellicle, which frequently consists of a practically pure culture of the organism. The cholera-red reaction may be obtained in pepton solution after from six to twelve hours' growth at 37° C. This color is developed by the addition of a few drops of pure sulphuric acid to the culture and is due to the presence of indol.

Specific serum easily obtained by the previous treatment of rabbits or other animals with the vibrio is valuable for diagnostic purposes and agglutinates the vibrio in high dilution. In order to prepare such a serum repeated doses of living cholera bacilli are injected intravenously into rabbits at intervals of two or three days. Seven days after the last injection the animal is bled to death and the serum obtained may be preserved in sterile receptacles by the addition of 0.5 per cent carbolic acid. In this manner a serum which will agglutinate the cholera vibrio in dilutions as high as 1 to 15,000 may be obtained. Strong found that a single intravenous inoculation of a rabbit with the immunizing substances extracted from seventy milligrams of a virulent cholera organism furnishes a serum of sufficient value for all practical diagnostic purposes. Such sera generally show an agglutination value of from 1 to 1,000 to 1 to 2,000, sometimes falling as low as 1 to 800. The application of the agglutination test is relatively simple. Pepton water is inoculated with a small bit of the suspected feces and allowed to develop at 37° C. for six hours or longer. A subculture is made from this growth into the same medium and after this has developed, the application of the agglutination serum may be made.

Paracholeras.—By the employment of specific agglutinating sera it has been demonstrated that there are many strains of the cholera vibrio which may cause the disease. This matter has been investigated by Mackie and Storer in Egypt. Studying the bacteriology of a small epi-

demic at Alexandria, these investigators isolated two species which they proposed should be designated as *V. cholerae* A and B. Concerning these strains, the following statement is made:

"It will be seen from the bacteriologic description that these vibrio strains closely resemble in many of their characters the *V. cholerae* but that they are differentiated chiefly by their serologic reactions. As regards the general cultural characters any difference which exists is quantitative rather than qualitative; thus the liquefaction of gelatin and solidified serum is more marked and the growth of the various media more abundant. The biochemical characters are in general similar. Hemolytic test distinguishes these strains from the classical cholera vibrio, but, on the other hand, varieties of the cholera vibrio which respond to certain of the specific reactions have been shown to be hemolytic. * * * It has been disputed by various observers whether agglutinability of a cholera vibrio by an anticholera serum is a fixed and constant character. Thus it was shown by Cren-diropoulo how inagglutinability might occur in the human body; he found that agglutinable vibrios in the feces were succeeded after a time by agglutinable vibrios in the bile. Greig has shown how an inagglutinable water-vibrio after isolation from the bile from an experimental animal tended to alter its morphologic and serologic characters; so that it approached more closely to the standard *Vibrio cholerae*. Chalmers and Waterfield in a recent paper discussed fully the biologic classification of the various types of vibrios and concluded that the evidence was in favor of the agglutination test as a suitable means of differentiating the cholera group from other vibrios."

Greig has reported upon the examination of the stools in 659 cases of cholera at Calcutta. He found that the intravenous injection into rabbits of atypical cholera vibrios produced a serum which does not agglutinate the standard cholera vibrio, while it does agglutinate the atypical strain with which the animal has been treated. By this process he isolated 65 strains and was able to classify 62 of these in nine groups. In these groups he found that No. 2 was most frequently met with in the stools of cholera cases in Calcutta at the time of his investigation. It is too early to speak positively concerning the paracholera vibrios. It appears, however, that there are many atypical cholera vibrios and that these can be distinguished from the Koch organism and from one another by specific sera.

Cholera Carriers.—The importance of cholera carriers depends largely upon the possibility of the continued existence of the vibrios in the body after recovery from the disease. Greig has furnished the most important contributions to this subject. He says:

"If the cholera vibrio is an inhabitant of the intestine only and does not gain access to the biliary passages as stated in a standard textbook of bacteriology, a view which is very generally held at present, then the conditions for the prolonged life of the organism in the body of the host after recovery from the acute attack would be much less favorable, as the delicate comma bacillus would have to enter into a struggle with the other intestinal and putrefactive organisms, and that too in an unfavorable medium. Although an acute or temporary carrier might result,

the possibility of a permanent chronic cholera carrier being produced in these circumstances would be slight. On the other hand, if it can enter the gall bladder it finds there ideal conditions for its prolonged life, namely, the absence of other competitors and a suitable alkaline medium; indeed, Ottolenghi has recently recommended bile as a selective medium for enriching the comma bacillus in place of pepton water and I can confirm the value of this medium from my experience. My researches have demonstrated that the cholera vibrio can enter and live in the bile, and the fact that it does so increases the chances of the production of the chronic cholera carrier. From the point of view of the prevention of cholera the chronic carrier is a much more serious problem to deal with than an acute carrier, although the latter is by no means without significance and both deserve close consideration. An apparently healthy person, whether convalescent or contact, harboring the cholera vibrio in the gall bladder, is dangerous in a high degree, because he is liable to start fresh foci of infection, it may be in various widely separated places to which he may travel, and, possibly, retain in his body the organism of cholera for prolonged periods. Such a person acts as a reservoir of the virus. Owing to the fact that the recovery from cholera is remarkably fast and that the patients are, as a rule, discharged at the first opportunity from hospital, there is much greater danger in this disease of highly infective persons returning to the community than in enteric fever, in which the convalescence is slower."

So keen an observer as Rogers, stated in 1911 that the absence of infection of the gall bladder and bile ducts by the comma bacillus placed the disease in this respect in quite a different position from that of typhoid fever. It seems, however, that later and more careful investigation has shown that Rogers was in error in making this statement. Greig found from his studies that 3.6 per cent of cases of cholera in India are discharged from hospital in an infective condition. Furthermore, he has traced local outbreaks to carriers. While the statement is generally made that cholera bacilli do not penetrate the intestinal walls and reach the blood or lymph, Greig has found the comma bacillus in the urine in eight cases out of 55 in which this test was made. It follows from this that the danger of the cholera carrier to the communities which he visits is comparable with that of the typhoid carrier. The length of time during which the vibrio can be recovered from the stools of those convalescing from this disease is variable. Reporters on this point give the time as ranging from a few up to 90 days. During the epidemic in Petrograd in 1910 the proportion of carriers reached six per cent. Even higher figures have been recorded in Austria and Roumania, but these are based upon numbers too small to justify unquestioned acceptance. However, the epidemiologic importance of cholera carriers has evidently been underestimated in the past. According to Anderson, during the summer of 1911, 34,000 specimens of bowel discharges from passengers and crews from cholera infected ports were examined bacteriologically to detect cases of cholera or carriers. As a result, at the New York quarantine the cholera vibrio was isolated from 28 persons sick with the disease and from 27 who were apparently in

health. During the same summer seven cases of cholera were detected by bacteriologic examination at other ports in this country.

Quarantine Prevention.—The U. S. Public Health Service has rendered the people of this country a great good by the efficiency with which it has excluded this disease, which has repeatedly in recent years reached our ports of entry. Medical officers have been stationed at foreign ports tributary to infected districts. For instance, during 1911, U. S. Public Health officers were stationed at Naples and Genoa, cholera existing at both places at the time. All steerage passengers were detained and held under observation for five days before being permitted to embark for this country. Forty-one carriers were discovered among those seeking passage to our shores at Italian ports. All baggage was disinfected and the bringing of foodstuffs on ships by immigrants was prohibited. During the voyage two medical officers, the Italian emigrant commissioner and the ship's surgeon, kept all passengers, especially those in steerage, under observation, being equipped for making bacteriologic examination of the stools. The arrival at port in this country of cases of suspicious illness was reported and all steerage passengers from places infected with cholera were submitted to bacteriologic examination. In New York, ships from infected shores were held at quarantine stations and all cholera cases and carriers were transferred to Swinburne's Island, where the sick were kept until recovery and where no one was released until repeated examination showed that he was no longer a carrier. To these precautions we owe our freedom from this disease at a time during which it had been widespread in other parts of the world. In more recent years, and especially during the great war, our quarantine provision against the admission of cholera has been effective not only at our Atlantic ports, but on the Pacific Coast as well. During the years 1917-1919, cholera has prevailed more or less extensively in China, India, Japan, Persia, Palestine, the Dutch East Indies, Siam, and the Philippine Islands.

Fly-Borne Cholera.—Long before the discovery of the cholera bacillus it was suspected that the house-fly might be concerned in the distribution of this disease. In describing his experience with cholera which prevailed on the Island of Malta in 1850, Nicholas, an English naval surgeon, wrote as follows:

“My first impression of the possibility of the transfer of the disease by flies was derived from the observation of the manner in which these voracious creatures, present in great numbers, and having equal access to the dejections and food of the patients, gorged themselves indiscriminately and then disgorged themselves on the food and drinking utensils. In 1850, ‘the Superb’ in common with the rest of the Mediterranean squadron was at sea for nearly six months; during the greater part of the time she had cholera on board. On putting to sea, the flies were in great force; but after a time the flies gradually disappeared and the epidemic slowly subsided. On going into Malta Harbor, but without communicating with the shore,

the flies returned in greater force and cholera also with increased violence. After more cruising at sea the flies disappeared gradually with the subsidence of the disease."

In 1886 Jepson called attention to the fact that cholera is most abundant at times and places when and where house-flies most abound. In studying cholera in north China in 1902, Tsuzuki captured flies in houses where there were cholera patients and succeeded in isolating cholera vibrios from them. In 1892 a Russian physician isolated cholera bacteria from the dejections of flies. This observation has been repeated many times in different parts of the world. While great epidemics of Asiatic cholera are due to infected water-supply, sporadic cases are caused in many instances by contact, either direct or indirect, and in the latter the house-fly may play an important rôle.

Immunity.—What degree of immunity to this disease is afforded by one attack we do not know positively, but it is probably about the same as that observed in typhoid fever. Since we have learned that there are at least two or more species of the cholera vibrio and from our experience with typhoid and the paratyphoids, it is evident that no great reliance can be placed upon immunity conferred by one attack. It has been observed in cholera, as well as in typhoid fever, that visitors coming to localities with infected water-supplies are more likely to have and to succumb to the disease than the natives. Writing on this point, Brad-dock makes the following statement:

"There is immunity in Asiatic cholera as in yellow fever. In the latter, in the tropics, the nonimmunes are the newcomers to the country. It is also so with cholera. The people in Bangkok, a city of 600,000 people, bathe in filthy klongs or canals of the city, drink filthy water from babyhood, the custom being to bury persons dying of cholera instead of cremating them; and therefore the water is infected a great part of the year. Very few of the Siamese born and raised in Bangkok, get cholera, unless there is a general epidemic, but the visitors from the Malay Peninsula, the Chinese coolies from China, and the Laos and Karens from the north of Siam are the usual victims when moving to Bangkok or visiting the city, and this I quote from personal observation. There is always some cholera in Bangkok, but, of course, always worse in the dry season. At a time when there was no cholera in the city a governor of one of the Malay Provinces visited the town with a large retinue of Malay servants, who were used to the clear mountain streams of the Peninsula. In ten days the whole retinue were dead of cholera. * * * It is a common saying in the north of Siam, 'if you go to Bangkok you die.'"

We can hardly agree with the above-mentioned author that the immunity in Asiatic cholera is comparable to that induced by one attack of yellow fever. It is more likely comparable to the increased resistance induced by one attack of typhoid fever.

Period of Incubation.—We cannot speak positively on this point. There are wonderful stories told about the quickness with which death follows infection. However, the trouble in accepting these is that we

do not know when infection took place. The period of incubation is usually placed for quarantine purposes at five days. We only know that it is short, but there are reasons for believing that it may be ten days or even more in some cases. Undoubtedly, individuals may carry cholera bacilli in their intestines for a relatively long time before they succeed in supplanting the native inhabitants of this region, manifesting their supremacy and causing the disease.

Personal Prophylaxis.—It is quite safe to work and to live in a cholera infected locality so long as proper precautions are taken. Specific vaccination may be employed, although this is not absolutely essential. The main point is to take care that no food or drink except in a sterilized state be permitted to enter the body. All uncooked food and unboiled water should be prohibited. Fruits and vegetables unless thoroughly cooked are to be avoided altogether. Plates, knives, forks, spoons, etc., should be sterilized and all food and food receptacles should be brought to the table so hot that no vibrio could survive on them. As has been stated, during the summer of 1911 and more or less since that time, the chief Italian cities, especially Naples, Genoa, and Venice, have had more or less cholera. They have escaped great epidemics simply because their water-supplies are so located that contamination is almost impossible. All who are acquainted with the filth and squalor of certain parts of these cities are not surprised that the disease continues in these localities for months and even years in sporadic form. During the summer of 1911 thousands of first-class passengers traversed the Atlantic wholly ignorant of the fact that Asiatic cholera was present even then among the steerage passengers.

Eradication.—We are not justified in taking it for granted that Asiatic cholera is a disease of the past and that it will soon be blotted out of existence even in its original home. The endemic area of this disease has gradually extended and it is likely to continue to do so for some years to come. We can hope to exclude it, as has been done in the past, from our continental area, but that it will occur from time to time in the Philippines, and possibly in Hawaii, is more than probable. So far as we know, cholera was confined a little more than 100 years ago to Lower Bengal. It is now endemic over the greater part of British India. It appears annually in Farther India, Siam, Cochin-China, China, and Japan. It appears frequently in Persia, Asia Minor, Turkey, the Balkan States, Austria, and Russia. It has made frequent excursions into Russia, Poland, and Germany.

In 1919 Constantinople was threatened with invasion by cholera from Russian ports along the Black Sea. The French Government took hold of the matter and by quarantine, sanitation, and vaccination effectively checked the spread of the disease. Cholera, however, continued for some

time in Odessa and compelled Denekine to order complete vaccination of his troops. It is reported that the disease promptly ceased among the soldiers but continued in the civil population. In making the surveys connected with this work many cholera carriers were found.

In 1920 there was an outbreak of cholera at Bangkok, Siam. This was studied by Mendelson and Tait, who state that the city consists of two parts, one with a pure water-supply and the other with polluted water. The morbidity in the former was 1.4 and in the latter 9.4 per 1,000. In the section having the polluted water a heavy rainfall was followed by an increase in number of cases. This was probably due to the washing of surface pollution into the water-supply. Mendelson and Tait believe that contaminated food, especially that from fields fertilized with night soil, played an important part in the distribution of the disease. They found that a single dose of vaccine apparently did but little good, and it was difficult to induce the people to repeat the dose.

During the summer of 1921 cholera wrought havoc in certain parts of Russia, especially along the Lower Volga, 24,000 cases being officially reported in June, 1921. Roumania on the south, and Latvia, Esthonia, and Lithuania on the north, took precautions against the introduction of the disease, which consisted in inspection of trains from infected districts and vaccination. It appears, however, that in 1921 cholera did not spread widely over Russia. Vaccination was put into operation at Moscow and at other northern and western points through which travelers from the Lower Volga would pass.

In regard to the cholera in Russia in 1921, the Health Committee of the League of Nations makes the following statement:

"The epidemic of cholera, which at first spread with alarming rapidity and was responsible for some 140,000 cases during the first five months of the year, came to an end very suddenly in the middle of what is usually the epidemic season. No satisfactory explanation of this phenomenon has been advanced. An experimental enquiry, started by Professor Zlatogorov, has thrown no light upon the subject. It is impossible to say whether or not there will be a recrudescence next summer, but it looks as if we were in the presence of a regular cycle still on its increase. The graphs illustrate the evolution of cholera in Russia since 1914 and also the geographical distribution of the epidemic in the course of the current year. The graph shows an enormous rise of the curve in 1920 and a gradual increase since 1917. It must be realized that the drop in the year 1919 may have been due to the fact that the Russian official figures apply to different areas in the different years, for notifications were being received only from the area of the Soviet administration, and this area varied in any given year with the changing fortunes of civil war. The map of geographical distribution shows that the disease stopped short a considerable distance east of Odessa. The difficult transport situation in Russia assists in the localization of epidemics. Had railway traffic been normal, cholera would have spread westwards. It is surprising, however, that in spite of a fair traffic on the Volga the epidemic does not seem to have traveled very far by this route."

As these sheets are going through the press, we are informed by the Health Section of the League of Nations that between January 1 and August 19, 1922, there were reported in Russia 55,697 cases of Asiatic cholera. It seems justifiable to conclude that this disease has been endemic along the Volga.

Bibliography

- ANDERSON, JOHN F.: Jour. Am. Med. Assn., 1912, lviii, 1748.
BRADDOCK, CHARLES S.: Internat. Clin., 1914, iv, 69.
CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, New York, 1913, William Wood & Company.
CLEMOW, FRANK G.: The Geography of Disease, Cambridge University Press, 1903.
GREIG, E. D. W.: Indian Jour. Med. Res., 1914 to 1918, i to v.
HOWARD, L. O.: The House-Fly, New York, 1911, Frederick A. Stokes Company.
MACKIE, T. J., AND STORER, E. J.: Great Britain Roy. Army Med. Corps Jour., 1918, xxxi, 161.
MACNAMARA, C.: A Treatise on Asiatic Cholera, London, 1870.
MANSON, P.: Tropical Diseases, New York, 1914, William Wood & Company.

CHAPTER XIII

THE DYSENTERIES AND DIARRHEAS

Description.—The earliest medical records recognized two groups of diseases of the bowels. The Greek names given to these continue in use up to the present and bear the same general significance that they had in the time of Hippocrates. Diarrhea, from the Greek words meaning to flow through, was applied, and continues to be applied, to those diseases of the bowels which are characterized by overfrequent, abundant, and watery stools, without admixture of blood or mucus. Dysentery, from the Greek words meaning difficult and intestine, covers those diseases which are characterized by griping, painful stools containing blood and mucus. This distinction between diarrhea and dysentery was made even before the time of Greek civilization, and in a general way has continued to hold good ever since. Early in our era it was shown that the dysenteries are characterized by intestinal ulceration and that every hemorrhage from the bowels does not justify classifying the case as one of dysentery. Between the diarrheas and the dysenteries, especially so far as ulceration in the intestine is concerned, there are intermediate cases. These are denominated either as diarrheal dysenteries or dysenteric diarrheas. Under the word dysentery, used in the plural, we include all those diseases the essential lesions of which consist of intestinal ulcerations and the chief symptoms of which are griping, pain, and the discharge of fecal material containing mucus and blood. Etiologically, the dysenteries may be divided into many groups. The causal agents may be animal parasites or bacteria. It is customary to speak of protozoal and bacterial dysenteries. These constitute the great bulk of sporadic, endemic, and epidemic cases. On making a closer analysis, we find that there are several animal parasites, widely different in species, and numerous bacteria, distinguishable one from the others by cultural and biologic tests, all of which or any of which may cause a dysentery. In their latest edition (1919) Castellani and Chalmers classify dysenteries and dysenteric diarrheas as follows:

A. Dysenteries caused by Animal Parasites:

- (1) The Protozoal Dysenteries
- (2) The Platyhelminthic Dysenteries
- (3) The Nematelminthic Dysenteries
- (4) The Arthropodic Dysenteries

B. Dysenteries caused by Bacteria

C. Pseudodysenteries

Amoebic dysentery is also known as amoebiasis, entamoebiasis, entamoebic dysentery, amoebic enteritis, amoebic colitis, and Castellani and Chalmers use the terms loeschiasis and loeschial dysentery.

History.—In the most ancient medical records in India, notably those of Charaka and Susruta, dysenteric diseases are mentioned and described with sufficient detail to render their identification certain. In the aphorisms, Hippocrates says:

“Dysentery, if it commences with black bile, is mortal. * * * If in a person ill of dysentery, substances resembling flesh be discharged from the bowels, it is a mortal symptom. * * * Alvine dejections, which are black like blood, taking place spontaneously, either with or without fever, are very bad; and the more numerous and unfavorable the colors, so much the worse; when with medicine it is better, and a variety of colors in this case is not so bad. * * * In protracted cases of dysentery, loathing of food is a bad symptom, and still worse, if along with fever.”

In his prorrhethics, he says:

“Dysenteries, when they set in with fever, alvine discharges of a mixed character, or with inflammation of the liver or of the hypochondrium, or of the stomach, such as are painful, with retention of food and thirst, all these are bad, and the more of these symptoms there are, the greater the danger; and the fewer, the more hope is there of recovery. Children from five to ten years of age are the most apt to die of this complaint; the other ages less so. Such dysenteries as are of a beneficial nature, and are attended with blood and scrapings of the bowels, cease on the seventh or fourteenth, or twentieth or thirtieth day, or within that period. In such cases even a pregnant woman may recover and not suffer abortion.”

In discussing, in his books on epidemics, the diseases prevalent in one season, he says:

“Dysenteries were epidemical during the summer, and some of those cases in which the hemorrhage occurred, terminated in dysentery, as happened to the slave of Eraton, and to Mullus, who had a copious hemorrhage, which settled down into dysentery, and they recovered. * * * In most, the bowels were disordered with thin and bilious dejections, and many after passing through the other crises, terminated in dysenteries as happened to Xenophanes and Critias. * * * And many and serious complaints attacked many persons in the region of the belly. In the first place, tenesmus accompanied with pain, attacked many, but more especially children, and all who had not attained puberty, and the most of these died. There were many cases of lientery and of dysentery; but these were not attended with much pain. The evacuations were bilious, and fatty, and thin, and watery; in many instances the disease terminated in this way, with and without fever; there were painful tormina and volvuli of a malignant kind; copious evacuations of the contents of the guts, and yet much remained behind; and the passages did not carry off the pains, but yielded with difficulty to the means administered; for in most cases purgings were hurtful to those affected in this manner; many died speedily, but in many others they held out longer. In a word, all died, both those who had acute attacks, and those who had chronic, most especially from affections of the belly, for it was the belly which carried them all off.”

As to the seasonal prevalence of the dysenteries in Greece at his time, Hippocrates, in his book on “Airs, Waters and Places,” wrote as follows:

“And respecting the seasons, one may judge whether the year will prove sickly or healthy from the following observations: If the appearances connected with the rising and setting stars be as they should be; if there be rains in autumn; if the winter be mild, neither very tepid nor unseasonably cold, and if in spring the rains be seasonable, and so also in summer, the year is likely to prove healthy. But if the winter be dry and northerly, and the spring showery and southerly, the summer will necessarily be of a febrile character, and give rise to ophthalmies and dysenteries. For when suffocating heat sets in all of a sudden, while the earth is moistened by the vernal showers, and by the south wind, the heat is necessarily doubled from the earth, which is thus soaked by rain and heated by a burning sun, while, at the same time, men’s bellies are not in an orderly state, nor the brain properly dried; for it is impossible, after such a spring, but that the body and its flesh must be loaded with humors, so that very acute fevers will attack all, but especially those of a phlegmatic constitution. Dysenteries are also likely to occur to women and those of very humid temperament. And if at the rising of the Dogstar, rain and wintery storms supervene, and if the Etesian winds blow, there is reason to hope that these diseases will cease, and that the autumn will be healthy; but if not, it is likely to be a fatal season to children and women, but least of all to old men; and that convalescents will pass into quartans, and from quartans into dropsies; but if the winter be southerly, showery and mild, but the spring northerly, dry, and of a wintery character, in the first place women who happen to be with child, and whose accouchement should take place in spring, are apt to miscarry; and such as bring forth, have feeble and sickly children, so that they either die presently or are tender, feeble, and sickly, if they live. Such is the case with the women. The others are subject to dysenteries and dry ophthalmies, and some have catarrhs beginning in the head and descending to the lungs. Men of a phlegmatic temperament are likely to have dysenteries; and women, also, from the humidity of their nature, the phlegm descending downward from the brain; those who are bilious, too, have dry ophthalmies from the heat and dryness of their flesh; the aged, too, have catarrhs from their flabbiness and melting of the veins, so that some of them die suddenly and some become paralytic on the right side or the left.”

From the time of Hippocrates in the fifth century B.C. to that of Aretaeus, about the first century A.D., there seems to have been marked progress in the study of the lesions in dysentery, for the latter author wrote:

“The superior intestines, as far as the cecum, which are small and abound in bile, are called Cholades; from this spot the lower ones are thick and fleshy to the termination of the rectum. Ulcerations occur in the whole of them, and as all these forms of ulcers constitute dysentery, the affections are diverse. For some merely abrade the surface of the intestines, producing only an excoriation, and are not dangerous, though they are much less so, if the lower parts be affected, while deeper ones are not well conditioned. There are other deep ones which are not prominent, but are like glands, eating away, spreading and inclined to gangrene, which are fatal; the veins also become eroded, and in such there is more hemorrhagic oozing. There is another form of ulcers which have thickened edges, are rough, ragged, callous, like what we term knots in wood, which are difficult to cure, from not readily cicatrizing, being more inclined to pass into a state of solution. There are very many sources of dysentery, the important ones are indigestion, constantly catching cold, the eating of pungent substances like salad, of onion by itself, or garlic, feeding on stale rancid meat, which

is followed by indigestion, taking any unusual drink, and a beverage of must, or brewed liquor, or those things that are used in different places, as a substitute for wine; a blow also, cold, and the taking of cold liquors, give rise to these ulcerations. The dejections and the general attendants of these ulcers are various in different cases. When they are merely superficial, and from the upper intestines, they are thin, bilious, and devoid of smell, except what is natural to the bowels. From the jejunum, they are more copious, yellow, and offensive. Sometimes they are accompanied with food, which, though in a state of solution, is lumpy; sometimes there is an offensive smell when the ulcers are gangrenous, and sometimes merely that of scybala; from ulcers in the lower bowels, the discharges are watery, thin and inodorous; when the ulcers are deeper, the discharges are ichorous, reddish, like wine or water in which meat has been washed, sometimes these appearances present themselves alone, sometimes with the feces, and they may either pass out moist, in a state of solution in the surrounding liquid, free from bile and smell, or firm and dry, though slimy from what surrounds them. When the ulcerations are larger and smoother from the upper bowels, the discharges abound in bile, on account of the spot from whence and through which it passes, and they irritate the outlet, for the bile is acrid, and especially, if it proceed from an ulcer, is greasy and looks like fat. But in the deeper ones, which occur in the lower bowels, the blood is in a thick clot, mixed with pituitous matter, like bits of flesh, not much like fat, but shreds as it were of the intestines, or as if, indeed, whole pieces were intermixed; sometimes they come forth white, thick, slimy, like suet chopped in the surrounding liquid, these come from the rectum; occasionally they are merely slimy, causing itching, small, round, and irritating, producing frequent attempts at evacuation, and an inclination to stool, which is attended with comfort, though what passes is exceedingly small. This is called tenesmus. From the cecum there are also red and large pieces of flesh discharged, of much larger outline, the ulcers become deep, the blood thick, like lees, and more offensive than in the former cases. When the ulcers spread and corrode, and cannot be by any means checked, we have from the upper intestines, in addition to these copious and bilious excretions, yellow, frothy dejections, looking like wine lees, black, of the color of woad or leeks and thicker than the previous ones, offensive, like putrid matter, and the aliment is now less digested, as if it had been greedily masticated. When the lower bowels are corroded, the clots of blood are dark colored, thick, like pieces of flesh, red, grumous, and sometimes black, of all varieties, intolerably offensive, and the fluid matter is expelled involuntarily; sometimes a long distinct piece comes away, like the sound intestine; those who are ignorant of this feel alarmed about the bowel, but the case stands thus: there are in the bowels, as in the stomach, two coats, and these obliquely overlap each other, should what lies between them be dissolved, the inner coat comes away for its whole length, while the external one remains alone, granulates, and cicatrizes, and the patients get well and remain uninjured, the lower bowel only is thus affected, which is caused by the fleshy structure of its coats. When blood flows from any vessel, it comes away florid or dark colored, pure, unmixed with food or scybala, and a pellicle forms on the surface like a broad spider's web, and it becomes clotted when it gets cold; and the act of excretion does not give the notion of blood, for from the great rush and wind that accompanies it, the patients fancy it greater than is actually the case; sometimes purulent abscess occurs in the colon, and as frequently as other internal ulcers; the symptoms, the pus, and treatment of the ulcers are the same; if the excretions are hard, of fleshy matter, and as it were rubbed up with rough bodies, the abscess is not of a kindly sort; sometimes there is a copious

flow of water from the colon, like a dysenteric discharge, and this sort of dropsy has saved a vast number; such then, in short, are ulcers in the intestines, and such are their phenomena and excretions as I have described.

"I will now describe the symptoms in each affection, whether the ulcers are well or ill conditioned; to speak generally, whenever there is merely slight abrasion of the upper or lower bowels, the patients are free from fever and pain, and are cured without confinement to their bed, by keeping them variously on spare diet. But when there is ulceration in the upper bowels, there is a gnawing, sharp, twitching pain, as if from a small quantity of heated bile, and now and then, indeed for the most part, suppuration occurs; digestion is imperfect, but there is no loss of appetite. Ulcers in the lower bowels are much less dangerous than those in the upper, for the former are more fleshy than the latter; if, however, they become deep, and spread upwards into the superior intestines, acute fevers arise, hiding and obscurely lurking in the viscera, accompanied with great chilliness, and dislike of food, and watchfulness, there are offensive eructations, nausea, vomiting, bile, and dizziness, and if there be a copious discharge of bilious matter, there are continual gripings, and exacerbated pains in addition, strength fails, the knees totter, burning fever, thirst, anxiety, a black vomit, parched tongue, small, feeble pulse, symptoms akin to those that I have described as fatal, under the head of malignant ulcers, show themselves, the powers of the heart fail, till the patients swoon, and some never come to again but are wont thus to perish. The same formidable symptoms also attend erosions of the lower bowels if the ulcers spread, and the discharge cannot be checked, except that the gripings and pains occur where the ulcers are situated underneath the navel; the forms of the excretions are such as I have described. Where the ulcers are originally small, and are long checked in their spread, new crops succeed, some in a state of quiescence, others cresting to a head, like billows in the sea; such is the flood of ulcers; if then nature interpose her assistance, and the physician cooperate with her, their spread is stayed, and there is no fear of death, but the bowels remain hard and tuberculated, and the cure is tedious. Hemorrhage from the bowels, whether it be from an artery or large vein, produces speedy death, for it is not possible either to introduce the hand and relieve the pain, or make any medicinal application to the ulcer; and if the hemorrhage could be stopped by any medicine, still there would be no certain escape from death, for in some cases a crust falls, and occasions a larger aperture of the vein, whereupon clots form internally, which stop there and the disease is not to be got the better of; it is, therefore, our business to staunch incipient hemorrhage, and an impending attack is usually pretty clearly indicated, if it be not altogether obvious. There is anxiety and a sense of uneasiness, a weight in the part that is likely to rupture, and a redness of the face when no rupture has yet occurred, if the vessel be fresh ruptured, it may be usually perfectly stopped, but if this have occurred some time, it is a more difficult and tedious process; such, then are intestinal ulcers. They occur in summer, less frequently in the autumn, still less so in the spring, and least of all in the winter. Children and youths are subject to diarrhea; dysentery occurs to young men in the prime of life; in old age the ulcers are difficult of cure, being slow in cicatrizing, corroding ones are seldom found in old people, although hemorrhage occurs in advanced life."

We have made this long quotation from Aretaeus, who, according to the best authority, lived sometime during the first century A.D. As we read it, we wonder at the pathologic knowledge which it reveals, and we ask ourselves whether this could have been written by one who did not make frequent autopsies.

Galen, Celsus, Aurelianus, and other medical writers of the early centuries of our era, emphasized the frequency and the fatality of the dysenteries. Following Aretaeus, the stools were examined with the intention of locating, so far as possible, the intestinal ulceration. The evidence thus obtained must have been quite indefinite and many of the conclusions reached quite fallacious. This question of determining the location of the ulcer is discussed extensively by Alexander of Tralles, who wrote about 500 A.D. Hirsch states that the frequent references to the dysenteries by early writers

“serve to show that in all those periods dysentery was an important thing in medical practice and well known to the profession, although it cannot be ignored that the example of Galen gradually led ‘dysentery’ to have a wider meaning and to include intestinal fluxes of various kinds. Other evidence that dysentery was very common and widely spread in those times, in association with diarrhea, is found in the accounts of several of the war pestilences of antiquity, and in the notices of pestilence by the medieval historians and chroniclers, in whom we find mention of no disease, after plague and pestilential fever, more often than of dysentery. From all these references, as well as from the exceedingly numerous epidemiographical accounts by practitioners of the sixteenth, seventeenth, and eighteenth centuries, we may safely conclude that dysentery, at all times, just as at present, had the widest diffusion over the globe, that it had exempted no considerable part of the world from a national visitation, that hardly another disease can be placed beside it in that respect, and that we may accept the statement of Ayres, ‘of dysentery it may be said that where man is found, there will some of its forms appear.’ ”

In 1619 Bontius, physician to the Dutch Settlement at Batavia, wrote, in Latin, a treatise on the diseases of the East Indies. More than a century later this work was translated into English by a physician who does not give his name. We employ the English translation. This author treats of the dysenteries under three heads. He says:

“And first of the true dysentery, that horrible and destructive disease, which causes greater devastation in the Indies than any other malady whatever. The true dysentery, then is an ulceration of the intestines with a perpetual purging, at first, mucus, afterwards bloody, and lastly, purulent, intermixed with the very substance of the bowels, with intolerable pain and griping of the belly.”

Bontius thought that the causes of true dysentery were the heat and dryness of the climate, together with the eating of too much, and often unripe, fruit, and the drinking too heavily of arae.

In the opinion of Bontius, the hepatic flux is less dangerous than dysentery, inasmuch as it is seldom accompanied by ulceration of the intestine. The author is somewhat hazy in accounting for what he calls “hepatic flux.” He states that it is probably due to an acrimony of the blood, causing dilatation of the mouths of the blood vessels and the pouring of blood into the intestine. One gets the impression from reading this chapter in the book by Bontius, that he recognized, as had been

done by some of the earlier authors, that every case of bloody flux does not mean dysentery. It is more than likely that some cases of the hepatic flux which Bontius describes were nothing more than hemorrhoids.

Bontius makes a distinct disease of tenesmus. His statement runs as follows:

“The tenesmus is more dreaded in this country, than the dysentery, on account of the extreme uneasiness which attends it; and indeed, when it precedes that disorder, it is generally mortal; because all diseases that increase by succession, are likewise increased in virulence. But if it comes after the dysentery, the cure is more easy, as, then, it is only the remains of that disease, fretting the parts affected. A tenesmus is an ulceration of the *intestinum rectum*, with constant pain and a desire of going to stool, when first, a little mucus, mixed with some drops of blood, and afterwards purulent matter is discharged. * * * A procidentia ani is frequently brought on, as are also the hemorrhoids; and if the disease continues long, a dropsy, as I have often observed. Whence follows a decay of the body, and, after excruciating torments, death.”

Bontius closes his short chapter on tenesmus with the following quotation from Celsus:

“As in all fluxes of the belly, so especially in this (the tenesmus) it is necessary that a person go to stool, not from inclination, but necessity, that this delay may inure the intestines to a habit of sustaining their burden.”

It is worthy of remark that, under the head of cholera morbus, Bontius describes, as prevalent in the East Indies nearly one hundred years before Asiatic cholera became known to the world, an acute choleraic disease. We deem this of sufficient importance to take from this author the following short quotation:

“The cholera might, with some degree of reason be reckoned a salutary excretion; since such humors are discharged in it as if retained would prove prejudicial. However as by such excessive purgations, the animal spirits are exhausted, and the heart, the fountain of heat and life is overwhelmed with the putrid effluvia, those who are seized with this disorder generally die, and that so quickly as in the space of four and twenty hours at most. Such, among others, was the fate of Cornelius Van Royen, steward of the hospital of the sick, who being in perfect health at six in the evening, was suddenly seized with the cholera, and expired in terrible agony and convulsions before twelve o’clock at night; the violence and rapidity of the disorder surmounting the force of every remedy.”

Sydenham, in his medical observations, has described the dysenteries of the years 1669 to 1672 as they appeared in London. He wrote as follows:

“Gripes without stools (dry gripes) set in at the beginning of August, 1669, and they were quite as common as, if not commoner than, the dysentery of the same autumn. Sometimes they were attended with fever; sometimes not. The gripings of the dysentery of the season answered to the gripings of the present diseases. Both sorts were most severe; both sorts came on at intervals, and both sorts were unaccompanied by motions, either slimy or stercoraceous. The dry gripes went along with dysentery

throughout the whole autumn, and at the same rate; but, as stated above, they were not present during the remaining years of the present constitution. Now, as this form of gripes differed but little from the dysentery, either in its nature or treatment, I confine myself to the last-named disease.

“I observed that, now as ever, the epidemic dysentery set in at the beginning of autumn, and declined at the approach of winter. When, however, the character of the year was of preeminently dysenteric constitution, it attacked a few patients at any time; most, perhaps, at the beginning of the spring, or even earlier, if there was a sudden thaw. Few indeed suffered; yet those few have convinced me that, in a season so little dysenteric of itself, the state of things most conducive to the disease was the state just mentioned. So it was during the years of the predominance of the dysentery. At odd times, men were attacked even at the end of winter, or at the beginning of spring.

“The disease sets in with chills and shivers. After these come the heat of fever, then gripings of the belly, and lastly, stools. Occasionally there is no fever, in which case, the gripes lead the way, and the purging follows soon after. Great torment of the belly, and sinking of the intestines, whenever motions are passed, are constant; and these motions are frequent, as well as distressing, the bowels coming down as they take place. They are always more slimy than stercoraceous, feces being rarely present, and when present causing but little pain. With these slimy motions appear streaks of blood, though not always. Sometimes, indeed, there is no passage of any blood whatever from first to last. Notwithstanding, provided that the motions be frequent, slimy, and attended with griping, the disease is a true bloody flux, or dysentery. In the meantime the patient, if a young man, or if heated by cordials, is feverish. His tongue is whitish, and coated with a thick mucous fur; if the disease be violent, it is dry and black. The strength is depressed, the spirits are low, all the symptoms of an ill-conditioned fever are present. And there are not only great pain and distress, but there is danger also. Unless the treatment be skillful, life is in peril. The vital warmth, and the due spirits may be impaired by the frequency of the evacuation before the peccant matter can be ejected from the blood; hands and feet may turn cold; the patient may die as quickly as from an acute disease; and even if he escapes the fate this once, he may be exposed to numerous and distressing symptoms of different sorts. For instance, when the disease has made certain progress, there will appear in his motions, instead of the mere bloody filaments which were at first mixed up with the feces, pure blood, in large quantities, free from even mucus, and in every evacuation. This indicates the erosion of some of the larger vessels that spread over the intestines, and it threatens death. At times the intestines, from the force of the inflammation which has been produced by the overabundant afflux of hot and acrid matters upon the affected parts, have been struck with incurable gangrene. Apathae, too, towards the close of the disease, beset the inner parts of the mouth and the fauces, particularly when the body has been long overheated, and when the evacuation of the peccant matter has been checked by astringent remedies, administered before the application of cathartics. These are generally signs of imminent dissolution.

“If the patient get over the aforesaid symptoms, and if the disease be protracted, the intestines become affected successively downwards, until the whole mischief is forced down to the rectum, and ends in tenesmus. Then the effect of stercoraceous feces is wholly different from what it was in dysentery. It is intensely painful, the feces, as they pass, scrape the bowels in their tender state; whereas, the slimy dejections only irritate the rectum, whilst the matter which is there, and there alone engendered is evacuated. This disease, although not infrequently fatal to adults, and still

more so to old men, is nevertheless exceedingly harmless with infants. They will bear it for months together without suffering, provided only that nature be left to herself."

It is worthy of observation that Sydenham saw, in epidemics of dysentery, the wave-like increase in virulence and the subsequent depression which are characteristic of epidemics in general. On this point he wrote:

"Furthermore, it must be observed, that all epidemics, when they first leap into life, emerging from the lap of nature, as far, at least, as their essence is discoverable in their phenomena, are combined with a principle more spirituous and more subtle than that which they possess when they have grown their growth; and that, just as they decline from their strength, they become thick and humoral. Whatever may be those particles which are mixed with the atmosphere, which war against health, and which determine the epidemic constitution, it is certain that they have a greater power of action at the time of their first outbreak than at any time afterwards. During the first months of the prevalence of the plague scarcely a day past without some one being attacked by the contagion, being taken suddenly in the streets, being stricken wholly without warning, and dying at once; whilst, when the disease had come to maturity, no one was ever so suddenly prostrated, but what fever, and other symptoms gave him warning. From this it is abundantly clear, that the disease was more violent and acute in its infancy, than it was at a later stage. It killed, to be sure, fewer; but then it killed them by means of a more violent influence on the system.

"It was the same with the flux. The earlier the stage the worse the symptoms. Looking, indeed, to the *number* of persons afflicted, *that* increased as the disease approached its climax, or status, and, for that reason, more died of it than at its beginning. But looking at the severity of the symptoms, *they* were the worst at the onset; worse, then, than at the status, and worse, then, than during the decline."

Cleghorn, an English army surgeon stationed at Minorca, has given an account of the diseases prevalent in that Island from 1744 to 1749, and in this account he includes dysentery. He gives no information as to the etiology of this disease, except that, in his opinion, one form of dysentery is due to the passage from the stomach into the intestines of undigested substances. This causes an increased secretion and flow of bile, leading to an abnormal washing away or removal of the mucus-protecting surface of the lumen of the intestines. The intestinal walls, being deprived of their protective mucous coat, are eroded and finally ulcerated, leading to griping pains and bloody stools.

Cleghorn's second form of dysentery begins suddenly, with chills, fever, and all the train of symptoms that ushers in most of the acute diseases. These preliminary symptoms are followed promptly by griping, tenesmus, and the evacuation of bloody, and possibly purulent, stools. In his third group of dysenteries, the first symptom is a twitching, which generally begins in the small intestines. This pain, as if the bowels were being drawn into knots, descends, involves the large intestine, and reaches the rectum; and this also results in dysenteric stools. According to Cleghorn, it matters not in which of these ways

dysentery begins; in process of time the case comes pretty much to the same state. The intestines are irritated, inflamed and ulcerated; a fever, for the most part of the periodical kind, comes on; the constant stimulus in the bowels diminishes the cutaneous discharges; a greater proportion of fluid is thrown into the intestines; the flux increases; the discharges become more purulent; the strength decays, and death or tedious recovery is commonly the consequence.

Cleghorn autopsied many of his cases and found ulcers, small abscesses and inflammatory areas in various parts of the intestine, but most abundantly and most markedly in the lower intestines and in the rectum. This author gives most of his space to treatment and, while it is not within the scope of a work on epidemiology to deal with the treatment of disease, we cannot refrain from calling attention to the fact that, periodically, some one discovers that ipecac is a valuable agent in the treatment of dysentery. Cleghorn used ipecac, gave it preference over any other drug, and recognized the fact that it was used in this disease long before his time.

Pringle, in describing the diseases of English soldiers in the camps in Flanders about the middle of the eighteenth century, dwells quite extensively on dysentery. The observations recorded by Pringle are in exact accord with those noted by other army surgeons, both before and after him. He states that when an army is first assembled there are likely to be among the men a few cases of dysentery, but they are not numerous and the disease is not highly virulent. This means that dysentery, at that time at least, was sufficiently disseminated among the people that sporadic cases were constantly being brought by enlistments into military organizations. The etiologic agents of the disease are excreted from the body in the stools. In the camp, the infected stools are distributed in the latrines and more or less widely scattered over the surface of the ground. Pringle notes that the disease is especially likely to occur in fixed camps. This means that continued occupation of a given location, for a time which varies with the location of the place, the nature of the soil, the number of people occupying it, and other factors, is necessary in order to get widespread pollution. This is why dysentery and typhoid fever are more prevalent in fixed camps than among moving soldiers. The more frequently the camp is moved the less is the pollution of the soil in any given locality. Dysentery spreads among the soldiers during the summer time, because the extracorporeal existence of the etiologic factor is favored by this season. Some of the organisms which cause dysentery may, and probably do, grow outside the animal body in fecal matter. Multiplication undoubtedly occurs at summer temperature. The infecting agents are carried, scattered, and deposited upon food by flies and other insects; in fact,

a fixed camp is a nursery in which the virus of dysentery may be grown most abundantly and may be spread most widely. A fixed camp is an incubator for the growth of many of the bacteria and protozoa which may cause dysentery. Pringle fully recognized the fact that dysentery is a transmissible disease, but, as to the manner of its transmission his ideas were vague. Probably it will be best to permit the author to speak for himself as to the causes of dysentery and its modes of transmission. He wrote as follows:

“The heat and moisture of the air appear to be no less the chief remote and external cause of the dysentery, than of the autumnal remitting and intermitting fevers; and therefore when other circumstances are equal, it usually prevails in the camp towards the end of summer, or in autumn, after great and continued heats, which, as was shown above, are generally attended with a loaded atmosphere. Upon comparing the account which I have given of the flux that occurred in every campaign with the description of the same distemper by other authors, we shall find this principle sufficiently verified. Sydenham indeed, in the history of the epidemic dysentery of his time, takes no notice of the weather, going, I must say, upon a false principle, that the morbid constitution of the season has never any connection with the sensible qualities of the air. But Willis supplies this defect, and observes that the summer of 1670 (which preceded the autumn wherein the flux was at its greatest height) was remarkably hot. In the year 1762, the summer heats and drought were of a longer continuance than I remember to have observed them in this country; and accordingly in autumn, the dysentery was so frequent in London, that though it could not be properly called epidemic, when compared to those fluxes which I have seen in the army, yet I believe that more cases occurred then, than in all the sixteen years that I had resided here. However, I do not advance this as a rule without exception; for that epidemic which raged at Nimeguen, in autumn 1736, came after a summer that was warm indeed, but to no extraordinary degree; and then none of the neighboring towns suffered, unless by their communication with the place infected. When the question is about a remote and external cause, it is to be understood, that however prevalent it may be, it is not sufficient to produce an effect, without a concurrence of the occasional or exciting causes; and that when these last, to be afterwards mentioned, are strong, they will sometimes produce the effect, independently of other causes.

“Corresponding to the remote external, is the internal predisposing cause, namely, a more than ordinary putrescent state of the blood, from a constant exposition to the sun in the hottest weather. We may likewise observe, that our men not caring to eat vegetables, and not being able to afford the price of fermented liquors, were in such circumstances deprived of two considerable antiseptics. For in general it may be remarked, that this disease *caeteris paribus* prevails mostly among such as are of a scorbutic (that is a putrid) habit, or among the poorer people, who from their foul air, bad diet, and nastiness, are most liable to putrid diseases. And there is an old observation, that such seasons as produced most flies, caterpillars, and other insects (whose increase depends so much on heat and moisture, and consequently on corruption) have likewise been most productive of the dysentery.

“Hitherto we have seen how similar the causes are of the remitting and intermitting fevers, and of the bloody flux. Nay, the affinity extends even to the occasional or exciting causes; such, as when in the end of summer, or in autumn, the men are exposed to night damps and fogs, especially after a hot day, or lie upon wet ground, or in wet clothes, part of them will be seized with that kind of fever, and part with

this flux; and perhaps some of them will have a disorder compounded of both. Add to this, that those fevers begin to be frequent in camp whilst dysentery still subsists; that the first symptoms are often similar, such as the rigors, and disorder of the stomach; that the remitting and intermitting fevers of a more malignant kind have sometimes ended in a bloody flux; that such countries as are most subject to these autumnal fevers, are likewise most liable to the dysentery; and that the analogy continues even to the method of cure, insofar as the principal part of it consists in clearing the *primæ viæ*. Upon the whole, the nature of the two distempers appears so much alike, that at first sight Sydenham seems to have expressed himself justly, when he called this flux, 'the fever of the season turned upon the bowels.' But upon a nearer view, we shall find this notion more acute than solid, since the circumstance of its being contagious shows that the dysentery is essentially different from these fevers. Degner offers good reasons for believing, that the fatal dysentery at Nimeguen was owing to the infection communicated by one person; and if the strangers suffered so little, in particular the Jews, we must ascribe that circumstance to the small intercourse which they had with the people of the place.

"In camp, the contagion passes from one who is ill, to his companions in the same tent, and from thence perhaps to the next.

"The foul straw becomes infectious. But the greater source of infection seems to be the privies, after they have received the dysenteric excrements of those who first fall ill. The hospitals likewise spread it; for those who are admitted with the flux, not only give it to the rest of the patients, but to the nurses and other attendants on the sick.

"In general, the contagion is not suddenly diffused. For whole towns and camps are never seized at once by the impurity of the atmosphere; but the infection is carried from one to another by the *effluvia*, or clothes, or bedding, etc., of the tainted person, as in the case of the plague, smallpox and measles. But the dysenteric *miasma* is of a less catching nature than any of these; so that in the milder epidemics it may pass unnoticed, as in those described by Sydenham and Willis, as we observed before.

"But of what nature is this infection? In the former editions of this work, I considered the spreading of the distemper as owing to putrid exhalations from the humors of those who fall first ill of it. And when this *miasma* is received into the blood, I conceived it to act upon the whole mass as a ferment, disposing it to putrefaction. But I am now sensible that this hypothesis would be insufficient, without proving at the same time, that when the blood is thus tainted, the vitiated part of it, by a certain law in the animal economy, must be thrown upon the intestines for excretion. This notion, of a putrid ferment, receives some confirmation from a case which occurred, of one who was seized (indeed in a slight degree) with a dysentery, accompanied with bloody stools, in making experiments upon human blood, which had become putrid by standing some months in a close phial. This case seemed the more decisive, as it happened at a time when the distemper was not heard of, and to a person in perfect health, who had formerly attended many dysenteric patients without being infected.

"For these reasons I was inclined to refer the *causa proxima*, or immediate cause of the disease, to this putrid ferment; but having since perused a curious dissertation published by Linnaeus in favor of Kircher's system of contagion by *animalcula*, I think it reasonable to suspend all *hypotheses* till that matter shall be further inquired into."

We have made this rather long quotation from Pringle's discussion of the causes of dysentery, because we believe that it is the most scientific

statement of the etiology of the dysenteries written up to that time (1768). Moreover, in our opinion, there was a retrocession in the knowledge of the cause of dysentery after the time of Pringle extending through more than one hundred years. If during that period army surgeons had been familiar with Pringle's observations, the death rate from disease in many a campaign would not have been as great as it proved to be. While Pringle shows respect for Sydenham, he does not blindly follow that distinguished author as most medical writers did for 200 years after the death of the English Hippocrates. As we have seen, Sydenham described a dry dysentery, or, as he called it, dry gripes, in which there was no departure from the normal in frequency of stool, in the composition of the evacuated matter, or in the symptoms attending defecation. Pringle, very properly in our opinion, denied the possibility of the existence of such a form of dysentery. Sydenham does not make dysentery a seasonal disease and, indeed, one who reads this great author, must come to the conclusion that he paid but little attention to the relation between the dysenteries and the weather. Sydenham did not regard dysentery as a contagious or transmissible disease, while Pringle was evidently convinced of the contagious nature of the disease. In the quotation, it will be observed Pringle says that dysentery prevails in those seasons when flies and other insects are most abundant. We infer from the reading of this paragraph that he believed the same seasonal conditions which favored the development of insects were likewise favorable to the development of dysentery. It does not appear that he suspected flies or other insects might be agents in the transmission of dysentery. Pringle's discussion of the relation between the dysenteries and the malarial fevers, if we interpret it correctly, is still sound. On this point also, he differs from Sydenham. The latter believed that the dysenteries result from seasonal fevers (malarial fevers) "turned upon the bowels." Pringle evidently believed that the malarial fevers and the dysenteries are distinct diseases, and certainly different in their etiology. He recognized the fact that having malarial fever did not give one immunity to dysentery and vice versa, and that the two diseases might, and often did, manifest themselves simultaneously in the same individual.

During our Civil War (1861-1865) many of our distinguished army surgeons were quite decidedly of the opinion that the "bloody flux" was of malarial origin, and this opinion has not wholly disappeared from the medical world today. Pringle's statement concerning the transmission of dysentery and the contagious nature of the disease forecast discoveries, some of which at least, had to await more than 100 years for their complete demonstration. He wrote that in camp the contagion passes from one soldier to his companions in the same tent. This

statement did not find its complete demonstration until the investigations by the Typhoid Commission were made in 1898, and this was not based upon studies of dysentery, but upon typhoid studies. In his observations that bedding, clothes, tentage, etc., became bearers of this contagion, he preceded the scientific demonstration of this fact by more than a century. He was quite convinced that latrines and other receptacles and deposits for fecal matter were connected in some way with the distribution of the disease. He certainly had it in his mind that the discharges from the bowels of the sick contained and carried to the outer world for distribution, the virus of the disease. At first, Pringle was inclined to adopt the generally accepted doctrine of the day and of all preceding time, that the virus consisted of an indefinite, indefinable, intangible miasm which floated in the air and was thus transmitted from the sick to the well; but it will be seen from the closing paragraph of the quotation that his logical mind was not convinced by this explanation, and the quotation closes with the statement that he suspends all hypotheses as to the nature of the contagion until further investigations have been made. With no desire to overemphasize or unduly stress the importance of Pringle's observations on dysentery, we are quite convinced that they constitute a marked advance in our knowledge of the dysenteries, and especially of these diseases as they at that time prevailed in camps.

Besides contributing to the etiology, Pringle's observations led to advances in the knowledge of the symptomatology, pathology, and treatment of the dysenteries. He made autopsies and tried to study the relations between the symptoms and the postmortem findings. As we have already seen, Aretaeus and many who came after him tried to locate the intestinal lesions during life from the nature and location of the pain and from the examination of the stools. We make the following quotation from Pringle on this point:

"It might be of use to know, what gut is particularly affected when the gripes are most severe. But this we can hardly ascertain, considering how much the intestines are liable to change their place by the peristaltic motion, how their situation may vary in different persons, and how readily the pain of the *colon* may be confounded with that of the smaller guts, which are surrounded by it. In general, the irritation of the stomach and higher intestines is attended with more sickness than gripes; and therefore, when the gripes are most acute without sickness, it is probable that the spasm is lower down. When the pain is about the middle of the belly, we may presume that the spasm is in the smaller intestines; but we cannot be certain, as in some subjects the upper flexure of the *colon* has been found as low as the umbilical region. Pains in the sides, back, and region of the kidneys, may be referred to the *colon*; but if the pains are felt towards the *os sacrum*, we may then suspect that the upper part of the *rectum* is affected. For the pain arising from the irritation of that gut may be referred equally to the back, and to the lower part of the belly; as a stone descending from the ureters is felt both ways, behind as well as before. But when the lower

extremity of the *rectum* is irritated, the spasm seems not then to be so much productive of pain as of a violent *nisus* drawing into consent the muscles of that part, as well as others which act in discharging the *feces*."

Annesley, in the thirties of the nineteenth century, wrote quite extensively concerning the diseases of India, including dysentery, of which he describes two forms as mostly prevalent—acute and hepatic dysentery. The former, according to his statement, was more prevalent among recent comers to India, while the latter caused a high death rate among English who had been some years in India. So far as the causation of the dysenteries is concerned, Annesley might have been a hundred years or more before Pringle instead of being one hundred years after him. The later author seems to have had no definite or intelligent ideas concerning the etiology of the dysenteries, as the following quotation will indicate:

"Of dysenteries as well as of fevers, it may be confidently stated, that all situations productive of terrestrial emanations, or malaria, and which furnish exhalations from the decay of animal and vegetable productions, under the operation of a moist and hot state of the atmosphere, will always occasion dysentery in the predisposed subject; and that the seasons of an intertropical country, in which a moist state of the air is conjoined with the greatest daily range or sudden vicissitudes of temperature, are those that are generally most conducive to the generation of this disease."

This author does think water might play some part in the causation of the dysenteries. He wrote:

"I have frequently remarked the very powerful influence of brackish water, and water which has been kept for a considerable time shut up from the air, and in a stagnant condition, and particularly from water taken from marshes, in the production of dysentery. I believe that the frequency of this disease amongst the crews of ships during the sixteenth and seventeenth centuries, especially in warm climates, was chiefly owing to the unwholesome nature of the water, acquired by being long kept excluded from the air in wooden casks. Water, under such circumstances, especially river water, soon acquires a putrid and very offensive smell, becomes thick and muddy, and abounds with animalcula."

In regard to the contagiousness of dysentery, Annesley wrote as follows:

"As the disease is met with in warm climates, it seldom or never proves contagious. I know of no instance in which it has proved itself such in India. This, doubtless, is owing to the circumstances under which it is usually met with in warm countries, to the causes whence it most frequently springs, and to the free ventilation and attention to cleanliness which are always observed when numerous cases of this disease are admitted into hospitals. Although it appears both endemically and epidemically, under circumstances favorable to its prevalence, yet no unequivocal case of communication of the disease from one person to another, who has not been subjected to the causes whence it usually proceeds, has been satisfactorily made out in India, during my practice in that country. I do not deny, however, that under circumstances of crowding together of the sick, want of ventilation, and inattention to cleanliness, or when it is complicated with typhoid and malignant fevers, it will not evince this property; in-

deed, that it should evince it, is conformable to the laws which seem to influence the human economy; and is only an example of the activity of one of the causes which I am convinced is amongst the most influential in producing the disease, namely, putrid animal emanations floating in a warm, stagnant, and moist atmosphere."

The nature, prevalence, causes, and the varieties of the alvine fluxes prevalent among the soldiers during our Civil War were recorded and described in a most masterly way by Woodward. These diseases were divided into acute and chronic diarrhea and acute and chronic dysentery. The figures showing cases and deaths from these diseases among white and colored troops are given in Table XVIII.

TABLE XVIII

	WHITE TROOPS, FROM MAY 1, 1861, TO JUNE 30, 1866		COLORED TROOPS, FROM JULY 1, 1863, TO JUNE 30, 1866		TOTAL	
	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS
Acute Diarrhea	1,155,226	2,923	113,801	1,368	1,269,027	4,291
Chronic Diarrhea	170,488	27,558	12,098	3,278	182,586	30,836
Acute Dysentery	233,812	4,084	25,259	1,492	259,071	5,576
Chronic Dysentery	25,670	3,229	2,781	626	28,451	3,855
Total	1,585,196	37,794	153,939	6,764	1,739,135	44,558

Woodward says that, great as these figures are, they are too small, and he estimates the total deaths from diarrhea and dysentery among the Federal troops during the war at 57,265. Among the white troops, there was one case of chronic for every six of acute diarrhea and one case of chronic for every nine of acute dysentery. Among the colored troops, there was one case of chronic for every nine of acute diarrhea and one of chronic to every nine of acute dysentery. It should be understood in making these statements that the number of acute cases reported is larger than the number of individual soldiers taken sick, for the simple reason that one individual may represent two or more cases. Among the white troops, there was one death to every 395 cases of acute diarrhea; one to every 57 cases of acute dysentery; one to every six of chronic diarrhea, and one to every eight of chronic dysentery. Among the colored troops, there was one to every 83 cases of acute diarrhea; one to every 17 of acute dysentery; one to every four of chronic diarrhea, and one to every four and one-half of chronic dysentery. In Woodward's opinion, the cases reported as chronic diarrhea and as chronic dysentery were due to the same cause, and were in reality cases of dysentery. He says:

"Numerous records of *postmortem* examinations show that the disease generally called chronic diarrhea was an affection of the large intestine, which was thickened, softened, and ulcerated, or covered with pseudomembrane, or both; that in short the lesions in the cases reported as chronic diarrhea were identical with those observed in the cases reported as chronic dysentery."

Table XIX shows the number of cases and deaths from diarrhea and dysentery among white troops for each year, with the annual ratio per 1,000 of mean strength, and the number of cases to each death:

TABLE XIX

	NUMBER OF CASES	NUMBER OF DEATHS	ANNUAL RATIO OF CASES PER 1000 OF MEAN STRENGTH	ANNUAL RATIO OF DEATHS PER 1000 OF MEAN STRENGTH	NUMBER OF CASES TO EACH DEATH
May and June, 1861	9,772	4
Year ending June 30, 1862	215,058	1,205	770	4.17	178
Year ending June 30, 1863	521,879	10,554	850	15.99	49
Year ending June 30, 1864	395,720	10,661	639	15.78	37
Year ending June 30, 1865	393,783	13,740	686	21.29	29
Year ending June 30, 1866	48,984	1,630	494	16.00	30

Commenting on the above table, Woodward writes:

"It will be observed that the ratio of deaths to strength during the second and third years of the war is about four times that of the first year; during the fourth year it was more than five times as great; and during the year following the war the mortality again diminished to about what it had been during the second and third years. It will also be seen, from the number of cases to each death as presented in the table, that the proportion of deaths to cases during the last year of the war was six times greater than it was during the first, and that the diminished mortality during the year following the war was due to a diminution in the number rather than in the severity of the cases."

These findings are in conformity with observations made concerning the prevalence of diarrhea and dysentery among troops in all parts of the world. At first assembly there are only a few cases and the death rate is low or there are no deaths. As time progresses and new recruits come in, the number of cases increases and the fatality greatly increases. After a still longer time, there may be no increase in the proportionate number of cases, but the case mortality continues to increase. An apparent exception to this was observed by Woodward among the colored troops. He wrote:

"In the case of the colored troops a similar increase in the total mortality from diarrhea and dysentery with the progress of the war is not observed. The ratio of deaths to strength is, in fact, greatest during the first year represented by the returns, and diminished during subsequent years. At first sight these results would appear to invalidate the explanation of the steadily increasing mortality from diarrhea and dysentery among the white troops which has just been offered, but, in fact, the circumstances under which most of the colored troops were first mustered into service were very different from those which surrounded the white. The recruits were largely found among the escaped slaves who accumulated in large numbers within the lines of our armies, and who had suffered much from exposure and privation before they enlisted. Moreover, from want of discipline and other causes, the hygienic conditions which at first prevailed in their camps were of the most unfavorable character. With subsequent

improvement in the discipline and hygienic management of the colored troops the mortality from diarrhea and dysentery progressively diminished."

Among both white and colored troops, and in all areas, diarrhea and dysentery were most frequent during the summer and autumn.

From fragmentary reports, Woodward concludes that diarrhea and dysentery caused nearly twice as much illness in the Confederate as among the Federal soldiers.

"So far as we can ascertain, the mortality from these diseases among the prisoners held by the Confederates amounted to more than half of all the deaths from disease."

From March to August, 1864, the number of prisoners held at Andersonville, Ga., varied from 7,500 in March to 32,899 in August. In September of that year a Confederate medical officer, Jones, made a report upon conditions in this prison, from which we make the following quotation:

"During the six months, 12,090 cases and 3,530 deaths from acute and chronic diarrhea, and 4,682 cases and 999 deaths from acute and chronic dysentery, were recorded. The cases of diarrhea and dysentery together numbered 16,772, or nearly one-half of the total number of sick and wounded. The deaths caused by these two diseases are recorded at 4,529, or, in other words, these diseases caused more than one-half, or more exactly 58.7 per cent, of all the deaths. These figures are below the truth. As far as my personal examinations extended, almost every prisoner was affected with either diarrhea or dysentery."

Woodward gives the following description of the prison at Andersonville:

"Camp Sumter, as the depot was designated by the Confederate authorities, was situated about half a mile from Andersonville station, on the southwestern railroad leading from Macon to Americus, Ga. Originally about 17 acres of ground were enclosed by a stockade of pine logs 20 feet high. The first prisoners arrived in February, 1864; by April there were 10,000. In July, the number of prisoners being above 29,000, and more being expected, the stockade was enlarged to an area of 23 acres and a half. Through this enclosure flowed a sluggish stream of water about six feet in width, bordered on each side by a low swamp, which occupied six acres of the narrow territory allotted to the prisoners. Into this stream and swamp the drainage of the camp took place, and the stream was at the same time the chief source of water-supply. No shelter was provided by the Confederate authorities except for the hospital, but some of the prisoners contrived to build huts of pine boughs roofed with pieces of shelter tents, while others burrowed in the ground. There is conclusive evidence that the rations furnished were of poor quality and insufficient in quantity. Unbolted corn meal was chiefly used instead of flour, and the fragments of husk which it contained seemed to aggravate the tendency to diarrhea and dysentery. A scorbutic condition of the system was consequently almost universal. The hospital accommodations were most meager and inadequate. At first a corner of the stockade was set aside for the purpose. In the latter part of May the hospital was removed to a point outside of the southwest angle of the prison enclosure. Here, in a space of about five acres, nearly 2,000 sick were scantily sheltered by old and ragged tents. The number of bunks was insufficient, and many of the patients lay on the ground without even a blanket. The

mortality which prevailed was the inevitable result of overcrowding, exposure, and starvation.’’

In no northern prison at any time were there as many prisoners as there were at Andersonville. Besides, in the North there was no reason that the rations should be so restricted as they were at Andersonville. Considering the smaller number in any one prison in the North and comparing the conditions existing in the North and in the South, Confederate prisoners in the North fared but little better, so far as diarrhea and dysentery were concerned, as is shown by the following report taken from Woodward, of the conditions at Camp Chase:

“The monthly reports of sick and wounded for the depot of prisoners at Camp Chase near Columbus, Ohio, commence May 20, 1863, when 500 prisoners were reported at the post. There were at that time a large number of paroled United States soldiers at Camp Chase, and the sick reports include the sick among them and the guard, as well as among the prisoners. After the first of February, 1864, separate sick reports were made for the prisoners. Prior to that time there is no means of ascertaining the number of cases among them; but the deaths were recorded by name, and were 131 in number. Of these, four died of wounds, 38 of diarrhea and dysentery, 25 of typhoid fever, and 19 of pneumonia. The separate reports extend from February, 1864, to June, 1865, inclusive, a period of 17 months. The mean number of prisoners present was 3,570; the greatest mean number for any one month was 7,760, during February, 1865. During the period of 17 months covered by the reports there were 4,063 cases of diarrhea and dysentery and 226 deaths, being at the rate of 803 cases and 44.69 deaths per 1,000 of mean strength annually.’’

While Woodward’s report is satisfactory so far as the symptomatology and the pathology of these diseases are concerned, his chapter on the causes of diarrhea and dysentery shows that he was quite as ignorant of these matters as was Aretaeus, who wrote in the first century of the Christian era. Woodward considers the insoluble and soluble constituents of drinking water, vegetable and animal contamination, and finds that none of these satisfactorily explains the prevalence of diarrhea and dysentery. He was halfway convinced that the virus of these diseases is present in the stools of the sick, and in one or two places he almost hits upon the true cause of the wide prevalence of diarrhea and dysentery in the camps. He says:

“The graphic language of medical inspector Summers shows that, as late as the summer of 1863, the great western army under General Grant had not yet learned the lesson which Moses taught the Israelites, when he made it a religious duty to bury their excrement beneath the soil; and I know of no reason for believing this particular army to have been less cleanly than the others. Certainly, I myself often witnessed such scenes as Dr. Summers has described, in the vicinity of the camps of the Army of the Potomac, before Washington and on the Peninsula. It is true that army regulations directed sinks to be dug in the vicinity of every camp, and it was generally directed that each day’s deposits should be covered with earth. But it was long before the men learned to use the trenches exclusively, and they were too often so badly

managed that it was disgusting to use them. The brush and timber in the vicinity of the camps usually bore positive testimony to the common neglect of the regulations on this important subject. Where the water-supply was derived wholly or in part from shallow surface wells, these were not infrequently so situated that every rain must have washed into them more or less of the fecal matter that polluted the soil. Where camp sites were long occupied, additional sources of surface contamination were afforded by the offal of cattle slaughtered for food, which was too often imperfectly buried, and without due regard to any relation between the situation of the place of burial and the wells. The same remark applies to the burial of dead horses, but I believe rarely to dead men, who were, I think more faithfully and discreetly buried than in any other war of similar magnitude."

Although Woodward seldom speaks with positiveness, there are to be found in his voluminous reports some suggestions, the value of which has been more recently demonstrated. For instance, no less an authority than Virchow had taught that dysentery may be due to constipation and the consequent ammoniacal fermentation of fecal matter in the intestine. Woodward disposes of this error by showing statistically that dysentery in the great majority of cases is not preceded by constipation. He wrote:

"A soldier suffering merely from constipation, who receives a purgative from the regimental surgeon, is reported as a case of constipation if excused from duty. The number of such cases reported among the white troops during the five years ending June 30, 1866, was 145,960. These figures do not include any of those occurring in the hospital population, and of course represent only the more serious cases of constipation; yet the number is so large that their distribution by season and region must give a very just idea of the actual distribution of constipation among our troops. Now it is worthy of note that the ratios deduced from these figures do not show any agreement in the regional distribution of constipation with that of dysentery during the war."

It had been argued by no less an authority than the great English sanitarian, Parkes, that the suspended and soluble inorganic substances in the waters of rivers might be the true cause of dysentery. It is true that many others had shown this to be erroneous, but Woodward collected the evidence and finally disposed of the matter. He also convinced himself, though he is not altogether clear on this matter, that an army cannot rid itself of diarrhea and dysentery by changing its location. Furthermore, Woodward was quite convinced that there is no causal relation between malaria and dysentery. He wrote:

"Certainly in our own Civil War, although, as has already been shown in detail, the malarial regions suffered most, no district in which troops were massed for war purposes was exempt from the scourge (dysentery)."

Woodward asked himself, "Is dysentery contagious?" To this question he gives no well-defined or satisfactory answer. It must be understood that at that time contagion had a narrow meaning. It generally meant that a contagious disease is one which a susceptible individual

contracts on merely coming into the presence of the sick. As thus understood, dysentery is certainly not a contagious disease. Hundreds, and probably thousands, of soldiers with dysentery were furloughed home, and in no case could it be shown that an epidemic resulted in consequence of this. Woodward was not ready to admit that something might not be done in order to prevent diarrhea and dysentery in camps, but he did not have the exact knowledge necessary to enable him to say just what should be done. On this point he wrote:

“Still less can I admit that in the case of armies in times of war the prevalence of diarrhea and dysentery in the camps is of itself any necessary indication of the existence of a genuine epidemic or endemic influence over which human agencies could be hoped to exercise little or no control. Not recent investigations only, but the general tenor of all military medical history is thoroughly opposed to any such deplorable doctrine. On the contrary, a careful survey of the evidence seems fully to justify the belief that these diseases generally result from the simultaneous action upon large numbers of men of several of the predisposing and exciting causes which have been discussed; some of the most dangerous of which—contaminated drinking water, insufficient or faulty alimentation, camp filth of every kind, especially human excreta, and all the reckless exposures and fatigues which are not required by the actual necessities of the campaign—it is quite possible, even in the present state of our knowledge, for an intelligent medical staff to point out and a wise army administration to avoid.”

It seems strange to us now that of the thousands of bright, keen medical officers in our Civil War no one appears to have thought of the possibility of settling the question as to the presence of the virus of dysentery in the stools of the sick by animal experimentation. It must be remembered, however, that at the time of the Civil War, the first facts concerning the true nature of infection were being gathered in France by the work of Pasteur, Davaine, Villemin, and others. At that time bacteriology and its methods constituted a closed volume, the first pages of which had never been read. Army medical officers knew nothing about the microscope, except what possibly a few of them had read. This instrument was not found in any hospital, and the hospital laboratory other than that pertaining to pathology, did not exist. The miasmatic theory of the spread of disease still dominated and held in bondage the medical profession.

There is one great disappointment in Woodward's report. So far as diarrhea and dysentery are concerned, there was absolutely no epidemiologic study of value. For this there seems to have been no adequate excuse. Epidemiology is much older than bacteriology and, while the latter has been helpful to the former, it has not always been and is not even now, an essential helper. Hundreds of years before the Civil War, Helidæus, of Padua, had shown that dysentery might be transferred from the sick to the well by the use on both in proper sequence of clyster pipes not properly cleaned. It would have been

easy for some army surgeon to have injected dysenteric stools into the rectum of some animal, and it would have been altogether justifiable had this experiment been made upon man. The contagious or infectious nature of dysentery had been taught by Sennertus, van Swieten, Pringle, and by many others. Gilbert had shown that epidemic dysentery in the French army in 1807 was highly contagious, and he had made it quite certain that the virus is contained in the stools. It is true that the infectious nature of dysentery, even by some of those who held it, had been made to conform with the miasmatic theory, and this idea certainly had great influence on those who furnished the data for the history of diarrhea and dysentery in our Civil War.

During the Franco-German War (1870-1871) dysentery became a serious disease in both armies and in the civil populations of the besieged cities of Paris and Metz. Writing in January, 1871, Virchow said:

"The present war has shattered one dogma after another put forth by the credulous. First, that modern arms have rendered fortifications useless. Second, that a modern war must be of short duration. Third, that a modern war would be a duel between armies, while noncombatants of both countries would remain in peace and friendship. Finally, the dogma, that the plagues of field and camp belong only to history.

"At the beginning, the present war promised to fulfill these predictions. A series of great and apparently decisive battles carried the victorious armies into the heart of the enemy's country. The killed and wounded were left behind, but the soldiers in full health and vigor marched on. Soon all was changed. Open warfare was replaced by siege. The besieging armies about Paris and Metz and the besieged within these cities were greater than history had ever known under similar conditions. Then, the plagues of war grew in strength and volume. Around Metz, the ancient home of dysentery and typhus, these foes to health sprang into renewed growth. In the besieging army first dysentery and then typhus wrought havoc. The hospitals improvised in school buildings and public halls and the hastily constructed barracks for the sick were soon overfilled and an endless train bearing sick and dying began moving to the hospitals at home. By the middle of October more than 50,000 had been thus transferred. The fate of those within the city was no less deplorable. Of these more than 25,000 sick and wounded were found at the time of capitulation.

"From the army about Paris the first news was good. The health of the soldiers was according to the official bulletins excellent. Then, from private sources there came disquieting rumors: dysentery is there! typhus is there! Finally came the fearful epidemic of smallpox among the Parisians unprotected as they were by vaccination."

The greatest German physicians of that time, such as Virchow, Heubner, Seitz, and others, believed that dysentery is due to a miasm which arises from the soil of certain localities. They went back 50 years, even 100 years, to prove that there had been dysentery in and around Paris and Metz. Heubner wrote as follows:

"Attention has been turned with success, however, to certain peculiarities of the soil of those countries where dysentery is endemic. It has come to light that every-

where in the tropics there has been a close connection between dysentery and malignant intermittent and remittent fevers; that the fevers indeed in certain regions (Guyana) may make their appearance in the form of dysentery, and at times even with intermittent character. From these observations the suggestions naturally arose that the miasma of dysentery like that of malaria, depended on vegetable and animal material in swampy land. Even the well-known passage of Hippocrates suggests this idea, and various writers of the middle ages and modern time, especially the observers of tropical dysentery, and even those who are content with purely mechanical causes for dysentery in special cases, come back finally to miasma from the ground, when it is a question of the etiology of the affection.

“Even the dysentery of wars which may develop so rapidly among large masses of persons when they change their position does not contradict this idea. This dysentery is always dependent on situation. It develops itself only in such places as are peculiarly predisposed to it. In the last war (1870) Virchow and Seitz rightly called attention to the fact that dysentery developed into an epidemic chiefly in the camps around Paris and Metz; places that were already known to have been infested with endemic fever or dysentery.

“We may then adopt, as the cause of epidemic and endemic dysentery a miasma, which is developed under the influence of a tropical climate, or of one resembling a tropical climate, in a soil of a certain moist and perhaps swampy character; in an analogous way with malarial poison; i. e., under conditions which exist in some parts of the tropics every year,—in the temperate zones only from time to time. We must, however, not suppose that dysentery poison and malaria poison are identical, which is certainly not the case, for there are many fever regions where there is no dysentery.

* * * Indeed we know nothing more of this hypothetical miasma than what has been said. We do not know whether it is gaseous or corporeal, etc. The parasitic theory of Linnaeus, who considered dysentery to be itch of the intestine, had to be given up long ago.”

This idea of the evil genius of localities has come down to us from remote time, and evidently as late as 1870, dominated the epidemiologic conceptions of even so great a man as Virchow; indeed, this idea has prevailed at later periods. In our chapter on typhoid fever, we have called attention to the fact that intelligent officers believed that the fever prevailing in their camps was due to a miasm peculiar to that locality. It is still natural for man to attribute the ills that fall upon him to the locality in which they occur. He is slow to realize that through his own ignorance he may pollute and render insalubrious the fairest spots on earth.

During the Spanish-American and Boer Wars, dysentery was so overshadowed by typhoid fever that it received scant mention, and, indeed, we have no evidence that in either this country or in South Africa during these wars did dysentery play an important rôle. It is possible that the feeble and inadequate attempts that were made in camp sanitation during these wars played some part in the suppression of dysentery but were insufficient to have any marked effect upon the control of typhoid fever.

During the World War the prevalence of diarrhea and dysentery

varied greatly and directly with the efficiency with which sanitary regulations were carried out. In our home camps there was but little dysentery, due to the thoroughness with which the drinking water was chlorinated, excreta disposed of, and the camps kept clean. The highest annual morbidity rate from this disease among soldiers in this country occurred in October, 1917. This was not above three per 1,000, and at no time after this did the rate reach higher than 1.5 per 1,000. The highest points reached in 1918 in the camps in this country occurred in June and November. During every other month throughout the war the rate for dysentery morbidity in the camps in this country was less than one per 1,000. In the Expeditionary Forces there was a marked increase in this disease during the summer and fall of 1918 when our troops, along with our allies, were hastily pursuing the retreating German armies. As they fell back, our foes wholly neglected in some localities every pretense for the disposal of their excreta. The ground was covered with human dejecta, flies swarmed over the whole land, and our advance was both too rapid and too hazardous to admit of adequate attention either to drinking water or to the disposal of excreta. In his report for 1919, the Surgeon General says:

“Epidemic diarrhea with a considerable amount of dysentery and probably some unrecognized typhoid and paratyphoid fevers developed in various parts of France late in June (1918) appearing first in the more southern areas occupied by our troops, and wherever insanitary disposal of human wastes, fly breeding, and insufficient precautions in the preparation and serving of food prevailed. Immediately after the Chateau-Thierry offensive the troops suffered quite generally from diarrheal diseases, probably as many as seventy per cent having been so affected. This was inevitable under the conditions of a hard fought and prolonged battle which made even the elementary principles of sanitation impracticable of application. Inadequate and ill prepared food, chilling of the body at night, polluted water sources, and the plague of flies, which bred and fed upon human excreta everywhere exposed and upon the dead bodies of men and draft animals upon the battle fields, combined to produce a widely spread epidemic of diarrhea among which was a certain proportion of true dysentery and typhoid-paratyphoid infections. Most of the cases never reached a hospital or obtained medical treatment. Spontaneous recovery in a few days was the rule. The enthusiasm of the victorious forward movement of the troops carried many men out of reach of hospitalization, and a true measure of noneffectiveness from that epidemic can only be guessed. A small number of serious and persistent infections found their way through the evacuation hospitals to the base hospitals, and of these the great majority examined early in the course of their disease were found to be suffering from true dysentery caused by well recognized strains of bacilli. Fortunately the type of the infection was mild and very few deaths resulted from the entire epidemic. The disease prevailed during the warm weather while the fly breeding season continued. In a few favored places, where after medical care was combined with adequate physical equipment to avoid fecal exposure and pollution of food and water, only an occasional case of diarrhea developed and entire organizations escaped infection, but in the main the disease prevailed throughout the American Expeditionary Forces from July 1 to the middle of September.”

Elsewhere the same authority states:

"During the first part of August a singular diarrhea had afflicted all in the Marne country, French, Americans, Germans, and French civilians alike, this diarrhea being without tenesmus or temperature and the mortality nil. Sanitarians deemed it a fly-borne disease of dysenteric nature, for the entire country was infested with myriads of flies. At this time the bread supplied left much to be desired, for being baked by the flash method in large loaves the interior was raw dough in lumps and the loaves were permeated with mold. As a similar disease made its appearance in the Second American Army months later when the cold weather had destroyed all flies we are still in the dark as to the nature of the disease which, if dysenteric in type, is without doubt a mild and most singular manifestation of the disease, and it is but fair to term it camp diarrhea of unknown origin, as the water-supply was not implicated."

In a few camps in this country, and more frequently in France, even a temporary interruption of the chlorination of the drinking water was followed by cases of dysentery. In the camps in this country bacteriologic examinations of the drinking water were made so frequently that such interruptions were detected within a few hours at most. In some of the camps it was known that the untreated water contained dysentery bacilli, but the effectiveness of chlorination in their destruction was abundantly demonstrated.

Dysentery became a serious matter in the English Army in the Gallipoli campaign. Bartlett makes the following statement:

"The chief epidemic diseases were enteric and dysentery. During the last six months of 1915 the admissions (to No. 21 General Hospital at Alexandria) on the medical side were 5,300 in number. Seventeen hundred and twenty-three were classed as enteric; of these 98 died, giving a mortality of 5.688 per cent. Eleven hundred and forty-six cases were classed as dysentery. This number does not include patients admitted for wounds, etc., who were suffering from mild dysentery or who developed clinical dysentery subsequent to their admission. Nearly everybody on the Peninsula suffered from diarrhea and cases were not classed as dysentery unless there was tenesmus, and blood and mucus were passed, or unless pathogenic amoebae or dysentery bacilli were found in the feces. Fifty-six patients died from dysentery, giving a mortality of 4.886 per cent. This number does not include patients who died from wounds, etc., and were found to have dysenteric ulcers in the postmortem room. Thus more than half the medical cases during this period were classified as enteric or dysentery."

Bartlett reports that the great majority of cases seen in his hospital were amoebic. Out of 61 cases carefully autopsied, only five were found to be of bacillary origin. Bahr and Willmore, working in another hospital but drawing its patients from the same military organization, criticize the findings of Bartlett, and state that the dysentery most prevalent in the Gallipoli campaign was bacillary; indeed, these authors hold that amoebic dysentery is always sporadic and endemic, never epidemic; that all dysentery epidemics among troops in the field are bacillary, and that at least ninety-five per cent of the cases among white troops in the Gallipoli campaign are of bacillary origin. Bahr and Willmore

claim that Bartlett mistook *Entamoeba coli* for *Entamoeba histolytica* and that his bacteriologic studies were not sufficiently accurate to enable him to discover the specific bacilli. They hold that in armies all cases of diarrhea should be diagnosed as dysentery on the appearance of blood and mucus in the stools, but differentiation between amoebic and bacillary dysentery should be made before treatment has been employed, since, according to their belief, emetin is a specific for amoebic while the serum treatment is a specific for bacillary dysentery.

Ledingham has made a report upon dysentery in the British Army in Mesopotamia. The total number of cases reported during the year 1918 was 25,642. Dysentery was much more prevalent among British than in Indian troops, the minimal incidence for the former in the month of February being 10.9 per 10,000 and the maximal incidence in November, 85.3; while for the Indians, the minimal incidence was 5.6 and the maximal, 21.9. Among the Indian troops amoebic dysentery was much more prevalent, while bacillary dysentery was the prevailing form among the English troops. The Shiga bacillus was recovered in 45.3 per cent of 715 isolations, while the Flexner bacillus occurred in 54.7 per cent. The relation between fly prevalence and dysentery is emphasized by this author. During the first quarter of the year practically no flies were in evidence and dysentery was at a minimum. With the oncoming of flies dysentery showed a simultaneous increase. However, with the disappearance of flies in the fall there was not a proportional decrease in the prevalence of dysentery. The author supposes that the mass of fresh infection is established by the agency of flies; this leaves behind it a large amount of chronic infection which, aided by weather conditions, seems to maintain the dysentery and diarrhea incidence at a constant level until the next fly outburst initiates a crop of fresh infections.

In 1920 dysentery assumed extensive epidemic proportion in Petrograd. This epidemic was of an extremely virulent kind, the case mortality rate being as high as twenty-two per cent for adults and forty per cent for children.

Drawing upon the as yet unpublished report of the Surgeon General covering the entire period of participation of the United States in the World War, we note that among 4,128,478 men there occurred 4,738 cases of dysentery and 73 deaths. This represents a morbidity rate per 100,000 of 115 and a death rate of 1.8. Thus there was one case of dysentery for every 872 men and one death for every 56,700.

Amoebic Dysentery

History.—Although amoebae had been previously found in the stools of man by Lewis and Cunningham in India and by Lambl in Bohemia,

the first to make a study of the relation of these protozoa to dysentery was Löschi, of Petrograd, who, in 1875 made a report which has become classical. In November, 1873, Löschi found himself in charge of a peasant, twenty-four years old, whose history may be condensed as follows: The young man came from the Province of Archangel to Petrograd in the summer of 1871. He arrived at the Capital in health and had had no preceding disease of importance. A few weeks after coming to Petrograd he developed a severe and exhausting diarrhea, which continued for some months and caused an exhaustion so marked that he was unable to work. He returned to his home, where apparently he slowly but completely recovered. In May, 1873, he returned to Petrograd and was employed at a saw mill in the vicinity of the city. His work necessitated his standing in water during a part of the day in drawing logs up to the mill. Consequently, his feet were wet and cold during the greater part of each day. The diarrhea returned and the patient was sent to the hospital. At that time he was having from seven to nine watery evacuations, accompanied by marked tenesmus, each day. The stools were reddish-brown, watery, ill-smelling, and contained grayish-red clumps of mucus and pus, which were deposited on standing. Upon microscopic examination these clumps were found to consist chiefly of large amoebae. The protozoa could be seen to move, changing both their shape and their location. While resting they seemed to be globular and measurement showed a usual diameter of from 20 to 30 microns; in some instances as much as 35 microns. When the bodies were stretched in movement they attained a length of 60 microns. The organisms were apparently granular, showed a distinct nucleus and often vacuoles of variable size were in evidence. This patient remained under Löschi's observations from November, 1873, to March, 1874, when he died, after developing pleurisy followed by pneumonia. Autopsy showed thickening and ulceration of the mucous and submucous membranes of the large intestines. The ulcers were round but irregular in form and were from one-half to two centimeters in diameter. Besides active ulceration, there were scars showing that healing processes had gone on from time to time. In the ulcers and in the contents of the intestine the same amoebae which had been found almost constantly in the stools during life were abundantly in evidence. Löschi had observed during the course of the disease that the symptoms and the number of amoebae in the stools fluctuated simultaneously. When the pain grew less and the number of stools were decreased and more closely approached the normal in consistency and color, the number of amoebae decreased; while with exacerbations in the symptoms, the number increased.

Löschi appears to have made good use of the months of opportunity

offered him for the study of this case. Under a magnifying power of 500 diameters he sometimes found in a single field from 60 to 70 amoebae. He found that the addition of a solution of sulphate of quinin, 1-5,000, killed the organisms immediately. He tried the administration of quinin in the treatment of the case and for a time with apparent benefit, the amoebae decreasing in number and finally wholly disappearing, while the appetite and general condition of the patient markedly improved. This good effect was, however, only temporary. Comparative studies were made with the amoebae found in the stools and amoebae obtained from other sources. Especially was comparison made with *Amoeba princeps*, but the individuals of this species proved to be much larger than those found in the stools. Lösch was unable to identify his organism with any known amoeba, and on account of its being found in the stool he named it *Amoeba coli*. From one to two ounces of the fresh stool of the sick man was repeatedly injected, at intervals of three days, into the rectum and administered by the mouth, to three dogs. Within half an hour after each injection the animals vomited and purged. This however, was not attributed by Lösch to infection with the amoebae, but was believed to be due to putrefactive products in the injected fluid. Other than these, transitory effects did not appear in two of the animals. In the third, however, on the eighth day after the last injection, mucous and bloody stools, containing large numbers of the amoebae, appeared. The health of the dog was apparently not disturbed, and in the course of two weeks the abnormal condition of the stool had disappeared. The animal was then killed and section showed the mucous membrane of the rectum swollen, inflamed, covered with a thick bloody mucus and showing three ulcers. These were roundish, with diameters varying from 4 to 7 mm., and surrounded by swollen, highly inflamed mucous membrane. The ulcers and the contents of the rectum contained the amoebae in large numbers.

Lösch asked himself the following questions: (1) Were the amoebae the essential cause of the disease in his patient? (2) Did the amoebae appear in the intestine as a result or in consequence of the inflammation and ulceration due to other causes? (3) Was the presence of the amoebae accidental and without any direct relation to the disease? After his animal experimentation, Lösch came to the conclusion that his patient had suffered with dysentery before the amoebae found their way into the intestine. He thought, however, that the amoebae might have contributed to the gravity of the case.

In the light of subsequent studies, there can be no doubt that Lösch had under his observation the amoeba now known to be the cause of dysentery and designated as *Entamoeba histolytica*.

In 1883, while studying Asiatic cholera in Egypt and India, Koch made five autopsies on persons dead from dysentery, two of which were complicated with liver abscess. In the intestinal ulcers observed in these cases Koch reported "peculiar amoeboid structures, about one and one-half to two times as large as white corpuscles." This finding was only incidental to Koch's greater work at that time and he made no further studies of these amoeboid bodies and, in fact, did not publish these observations until 1887. The bodies observed by Koch could have been no other than *E. histolytica*.

Beginning in 1885, Kartulis, of Egypt, has made many contributions to our knowledge of amoebic dysentery. He has found amoebae in dysentery and in liver abscesses, thus confirming the earlier work done by Lewis, Cunningham, and Koch. Kartulis, especially in his earlier papers, did not distinguish between pathogenic and nonpathogenic amoebae; indeed, no one was able to do this at that time, and this must be borne in mind in reading the contributions made by this investigator. At one time he claimed to have grown amoebae in cultures made of infusions of fresh straw. We now know that if amoebae were ever grown on such a preparation they were certainly not of the pathogenic kind. Kartulis was able to infect cats by injecting into the rectum dysenteric stools, and by the same method in the same animals he was not able to induce dysentery by the injection of the bacteria present in these stools. He reported that the filtration of dysenteric stools through flannel removes the amoebae and that the filtrates thus obtained may be injected into cats without effect. This investigator was, so far as we know, the first (1904) to demonstrate the presence of amoebae in a brain abscess, a discovery which has been confirmed several times since.

Hlava (1887) was the first, so far as we know, to report an epidemic of amoebic dysentery. This physician had under his charge in an insane asylum 60 cases of dysentery, in all of which amoebae were found. The amoebae were the only constant constituents of the stools, being found in all cases, while the bacteria varied greatly. Hlava made animal experiments, injecting stools into the rectums of 17 dogs, with two positive results; in six cats with four positive results, and in eight rabbits, two chickens, and six guinea pigs, with no positive result. From his animal experiments, from the fact that the amoebae were found in the stools of all and that there was no bacterium common to all stools, Hlava concludes that the amoebae were the cause of the disease.

Councilman and Lafleur (1891) published the now classical monograph on the pathology of amoebic dysentery, in which they held that this disease is a clinical entity and is characterized by well-defined pathologic lesions. The material used was obtained from 14 cases of amoebic dysentery. They gave the name *Amoeba dysenteriae* to the

organism found in their cases. They made a careful study of the organism itself, and its identity with what is now known as *Entamoeba histolytica* is certain.

Councilman and Lafleur conclude their exhaustive study of this subject with the following statement:

“1st. Amoebic dysentery is a form of dysentery which etiologically, clinically, and anatomically should be regarded as a distinct disease. 2nd. We consider that, (a) the *Amoeba dysenteriae* has been shown to be the causative agent from its constant presence in the stools and in the anatomical lesions, and from the inoculation experiments of Kartulis. (b) Clinically the disease is characterized by the presence of amoebae in the stools, which in addition present physical characters different from those seen in the stools of other forms of dysentery, as noted above; by a variable onset, course, and duration of which the special features are periods of intermission alternating with exacerbations; and by a marked tendency to chronicity, with the production of a greater or less degree of anemia. (c) Anatomically, the disease is characterized by the production of ulcers in the colon which generally differ from those found in any other forms of dysentery. The ulceration is produced by infiltration of the submucous tissue and necrosis of the overlying mucous membrane, the ulcer in consequence having the undermined form. Frequently in addition to the ulcers there is infiltration of the submucous tissue without ulceration. In all of these lesions unless complicated by the action of bacteria there is absence of the products of purulent inflammation. 3rd. Abscess of the liver with or without involvement of the lung is a frequent complication, much more so than in any other form of dysentery. The involvement of the lung may early follow hepatic involvement and be detected by the occurrence of amoebae in the sputum before there is any evidence of liver abscess. These abscesses differ in their anatomical features from those produced by other causes. The chief difference is found in the absence of purulent inflammation, the abscess being caused by necrosis, softening and liquefaction of the tissue. In these liver abscesses the amoebae are not associated with any other organisms. 4th. The disease is widely distributed, and is found in most countries in Europe, in most parts of the United States and in the tropics everywhere. 5th. This is the form of dysentery which has been commonly called tropical dysentery.”

Kovács (1892) had under his charge two cases of amoebic dysentery and experimentally infected five kittens with the amoebae. In the intestines of the cats he found typical lesions, but was unable to grow the amoebae in cultures, which fact renders it quite certain that he had under observation *E. histolytica* which, up to the present time, has not been grown artificially.

Kruse and Pasquale (1894) confirmed the finding of Kartulis, that the pus obtained from a dysenteric liver abscess may be free from bacteria and still may be employed successfully in inducing dysentery in cats after rectal injection. Out of seven cats treated with bacteria-free pus from a liver abscess, three developed dysentery. This is an important observation, because it is practically impossible to eliminate the effects of bacteria when dysenteric stools are employed in infecting animals.

The studies of Kruse and Pasquale were begun in Italy and continued in Egypt. In Italy they occasionally found amoebae in the stools of persons in apparent health. In Egypt they soon recognized that there are at least two kinds of amoebae that may appear in the human stools, one of which is pathogenic, while the other is nonpathogenic. They proposed that the first should be called *Amoeba dysenteriae*, while the latter should be designated *Amoeba coli*. The pathogenic variety induces dysentery with intestinal ulceration in cats, while the nonpathogenic is without effect on these animals. Certain nonpathogenic amoebae may be cultivated artificially, while attempts to grow pathogenic amoebae in cultures have always failed. These investigators were quite convinced that, while a certain form of dysentery is due to amoebae, there are other dysenteries which cannot be attributed to these protozoa.

Harris, of Georgia (1894), was the first, and so far as we can ascertain the only one, to observe multiplication by fission of amoebae in the stools. After a close study, extending through three years, he was able to make this observation, the correctness of which has been demonstrated by subsequent investigation. Ordinarily, pathogenic amoebae multiply in the human body, and this process must occur very infrequently in the stools. This matter will again be referred to when we discuss the multiplication of pathogenic amoebae. A little later (1898) Harris collected the literature bearing upon this subject, reported 35 cases of his own, and described, in a manner unexcelled up to that time, the structure and life-history of this rhizopod. Later still (1903) this investigator reported that he had succeeded in inducing in puppies not only dysentery, but in some instances amoebic liver abscesses.

Quinke and Roos (1893) and Roos alone (1894) studied two cases at Kiel. One patient came from Sicily and had a severe form of the disease; the other was a native of Schleswig-Holstein and had lived in Kiel for four years. The amoebae found in the stools of these two cases were quite dissimilar, both in form and in pathogenicity. Those from the Sicilian had an average diameter of from 20 to 25 microns, while those from the native were slightly larger, averaging from 25 to 30 microns. The former were highly pathogenic to cats, causing marked intestinal ulceration, with all the symptoms of dysentery and terminating fatally, while the latter produced at most only a transitory diarrhea. The pathogenic forms were more active in their movements, as seen under the microscope, than the nonpathogenic. The case in the Italian was undoubtedly amoebic dysentery, while that in the German was probably bacterial dysentery and the amoebae in the stools most probably were not concerned in the causation of the disease. The pathogenic organisms were undoubtedly the same as those described by Lösch and now called

E. histolytica, while the latter were identical with the nonpathogenic forms first described by Lewis and Cunningham in India and later by Grassi and many others. The most important finding, however, made by Quinke and Roos, was the discovery of the encysted forms in the stools. Dobell speaks about the work of these investigators as follows:

“Although Quinke and Roos studied only a single case of amoebic dysentery, they studied it very carefully; and they controlled their observations by a study of the amoebae occurring in nondysenteric cases. The amoebae found in the patient suffering from dysentery are well described, and recognizably figured. The sharp demarcation between the ectoplasm and the endoplasm, the appearance of the nucleus, the frequent presence of red corpuscles in the cytoplasm, and the striking activity of the organism, are all noted. In their account of all these characters, Quinke and Roos confirmed the observations of Lösch, Kovács and other early workers. But in addition, they discovered the cysts of the parasite in the stools of their patient. They are described as rounded, refractile structures with a thin but definite wall, smaller than the active amoebae, and measuring 10 to 12 microns in diameter. By means of careful experiments they proved that a cat can be infected, and acquire amoebic dysentery with characteristic intestinal lesions, by causing it to swallow the cysts, or by injection of the active amoebae *per anum*. All these characters were emphasized as distinctive of the amoebae associated with dysentery in man, for they found that the other amoebae which they studied (in reality *E. coli*) differed in all the characters noted. They were sluggish, contained ingested foreign bodies, but never red corpuscles, formed larger cysts with a thicker wall, and were non-infective and nonpathogenic for cats. From their observations they drew the conclusion that man acquires his infection with the dysentery amoeba by swallowing its cysts—as they had shown to be possible in the case of the cat. The only thing of importance that Quinke and Roos failed to do was to investigate the cytological details of the amoebae and their cysts. They merely noted that the latter contained ‘nucleus-like structures,’ but they did not study these properly nor count them. Roos’ figures show cysts with one or two nuclei (indistinct in some), and indications of chromatoid bodies. In the matter of nomenclature they were unfortunate; for though they rightly identified their pathogenic amoeba with Lösch’s ‘*Amoeba coli*,’ they wrongly proposed to change its name to ‘*Amoeba coli felis*,’ on account of its pathogenicity for the cat.”

Huber (1903) came very near supplying the defect in the work of Quinke and Roos, as pointed out by Dobell, inasmuch as he did study the cysts and counted their nuclei, but he never went far enough in these investigations to be able to distinguish, by the number of nuclei in the cysts, between pathogenic and nonpathogenic amoebae.

Schaudinn (1903) in his great work on reproduction in certain rhizopods taught that the amoebae concerned in the causation of dysentery in man multiply by the formation of spores, and apparently he was ignorant of the importance and significance of encystation. Recent writers, especially Dobell, have accused Schaudinn of offering a highly imaginative account of sporulation in these amoebae and of greatly confusing the nomenclature of the amoebae found in man. For details along this line the reader is referred to the recent work by Dobell on the *Amoebae Living in Man*. Inasmuch as this has no special bearing upon

the epidemiology of amoebic dysentery, we shall not go into detail concerning Schaudinn's work or the influence it has had upon the investigations into the causation of amoebic dysentery; neither is it desirable to mention in this brief history, all the workers who have made contributions to this subject. However, to Schaudinn belongs the credit of first clearly differentiating between the pathogenic amoeba, causing dysentery, which he named *Entamoeba histolytica*, and the harmless amoeba frequently found in the human intestine, which he named *Entamoeba coli*. Craig was the first to confirm Schaudinn's work regarding these two amoebae and to show that *Entamoeba coli* is a common parasite of the healthy human intestine in all parts of the United States.

Walker (1911) and Walker and Sellards (1913) have apparently straightened out the tangled threads in the knotty problem of the causal relationship of amoebae to dysentery. Concerning this work, Dobell makes the following statement:

"In the very same year that Schaudinn's erroneous statements made their appearance, a real discovery was made by Huber (1903); but so great was the authority of Schaudinn, that Huber's work was—and is—almost completely ignored. Huber (1903) confirmed the observations of Quineke and Roos. He studied a typical case of amoebic dysentery, he saw the amoebae and their cysts, and he infected cats with the former *per rectum* and with the latter *per os*. He added the important observation that the cysts contain one, two, or four nuclei, but never more, and also chromatin masses and blocks, and can thus be distinguished from the cysts of the 'ordinary' amoeba (i. e., *E. coli* as described by Schaudinn). Huber told Schaudinn of his observations—which were perfectly correct—but neither the latter nor anybody else who knew of them seems to have attached any importance to them at the time. After Schaudinn's death the cysts were once more 'discovered' by Viereck (1907) and by Hartmann (1907), who regarded them as belonging to a new species of *entamoeba*—named by them respectively *E. tetragena* and *E. africana*. Elmassian (1909) again 'discovered' them two years later, and regarded them—together with the precystic amoebae which form them—as another new species, which he named *E. minuta*. These various 'discoveries,' and others made during this period, only served to add to the existing confusion. Quineke and Roos' observations were forgotten, Huber's were ignored—everybody looked for—and some found—the nonexistent development of *E. histolytica* described by Schaudinn. No real advance in our knowledge of the dysentery amoeba, took place until the work of Walker (1911) made its appearance, followed soon after by his later memoir, in collaboration with Sellards (1913), which solved most of the problems connected with *E. histolytica*.

"Walker (1911) first showed that *E. histolytica* and *E. coli* are quite distinct and easily separable species, though possessing a similar development. The first forms cysts containing, when mature, four nuclei; the second cysts containing eight nuclei. In the cysts of both, development occurs in a straight-forward manner by the repeated division of an originally single nucleus—without any 'autogamy' or other mysterious processes such as were described by Schaudinn. Then he showed that *E. histolytica*, *E. tetragena*, and *E. minuta*, are all different names for one and the same species. Finally, with Sellards (1913), he proved conclusively by experiments on human beings that man becomes infected by ingesting the cysts of these amoebae; and that infection with *E.*

histolytica may give rise to dysentery, while *E. coli* is harmless to its host. To Walker (1911, 1913) we also owe the conception no less than the discovery of the 'carrier' condition in *E. histolytica* infections—a conception which cleared up all the difficulties which previously prevented the life history and activities of this organism from being properly understood."

Walker studied the amoeba found in the Manila water-supply. He gives the following statement concerning this supply, and shows that it was probably at all times free from contamination with the feces of man:

"The Manila water-supply comes from an uninhabited watershed of the Mariquina River and its tributaries. The water is stored in a reservoir on the watershed by a dam constructed across a narrow gorge in the Mariquina Valley at Montalban about 24 kilometers from Manila. It is conducted from this reservoir in closed water mains to Manila, where it is distributed in branch mains and pipes to the various taps in the city. The water, therefore, is presumably free from fecal contamination and should contain only the normal amoebic fauna of that watershed."

This water was found to contain amoebae in abundance. These amoebae could be grown on artificial cultures. They were fed to men, under proper conditions, and found in all cases to be inert or incapable of inducing infection.

It may be remarked here parenthetically that, while up to the present (1922) no reliable protozoologist has claimed to grow entamoebae artificially, such a claim has recently (1920) been made by Yoshida. This investigator states that he has been able to separate the cysts from everything else living in the stools and that he has grown these cysts or the amoebae contained there in pure culture. The statements made by this author do not carry conviction and certainly need confirmation.

Walker next made amoebic cultures from healthy persons, from those with amoebic dysentery, and from two cases of amoebic liver abscess. These cultivable amoebae, even those from cases of amoebic dysentery and from amoebic liver abscess, were found to be inert.

In the third place, Walker made a microscopic study of the amoebae found in the intestinal tract of man, both in those apparently healthy and in dysenteric cases. This search led to the demonstration that there may be in the intestinal tract of man two kinds of amoebae, one of which can be grown on artificial cultures, while the other has not been so grown. The cultivable amoebae, whatever the source from which they have been obtained, are not pathogenic to man. Some of these amoebae which are not cultivable are pathogenic to man, while others are not. Of the two kinds of noncultivable amoebae, one forms cysts which never contain more than four nuclei, and these are pathogenic to man. The other group of noncultivable amoebae forms cysts containing eight or more nuclei, and these are not pathogenic to man. Having established these fundamental differences in the amoebae which may be found

in the intestine of man, Walker came to the conclusion that they should be divided into two genera, amoeba and entamoeba. Some at least, of the first genus are cultivable, while none of the second are. No one of the first genus is pathogenic to man. Some of the second genus are pathogenic, while others are nonpathogenic, to man. The pathogenic organisms can be distinguished from the nonpathogenic by microscopic examination of the cysts and the determination of the number of nuclei.

Walker stated his summary and conclusions (1911) as follows:

“(1) The amoeboid organisms found in the Manila water-supply belong to the genus *Amoeba* Ehrenberg. (2) The amoeboid organisms cultivable from the intestinal tract of man, both from healthy persons and from cases of amoebic dysentery, also belong to the genus *Amoeba* Ehrenberg. (3) The cultivable species of the genus *Amoeba* are not parasitic in the intestinal tract of man; when obtained in cultures from the intestines they probably are derived from cysts of amoeba that have been ingested with water or food and have passed unchanged through the intestinal tract. (4) The amoeboid organisms parasitic in the intestinal tract of man belong to a distinct genus, *Entamoeba* Casagrandi and Barbagallo. (5) The entamoebae are strict or obligatory parasites and are incapable of multiplication outside of the body of their host. They cannot be cultivated on Musgrave and Clegg's medium. (6) One non-pathogenic species of the genus *Entamoeba*, *Entamoeba coli* Schaudinn, parasitic in the intestinal tract of man, which includes *Entamoeba nipponica* Koidzumi and which develops cysts containing 8 nuclei, is recognized. (7) One presumably pathogenic species of the genus *Entamoeba*, *Entamoeba histolytica* Schaudinn, which includes *Entamoeba tetragena* Viereck, and which develops cysts containing 4 nuclei, is recognized. (8) A differential diagnosis of an infection with *Entamoeba coli* from an infection with *Entamoeba histolytica* can be made with the microscope. (9) An infection with either *Entamoeba coli* or *Entamoeba histolytica* must always come directly or indirectly from another infected person. (10) Water or uncooked food can transmit amoebic dysentery only when contaminated with fecal matter from a case of amoebic dysentery. (11) The infection with *Entamoeba histolytica* may persist for an indefinite period after the symptoms of amoebic dysentery have disappeared, during which time the resistant, encysted entamoeba may be passed in large numbers in the stools and constitute an important source of infection to others. Such persons are ‘carriers’ of amoebic dysentery, comparable to the ‘carriers’ of typhoid fever or cholera. (12) The prophylactic measures for the prevention of amoebic dysentery are sufficiently indicated by the preceding conclusion; they are identical with those required for the prevention of other specific infectious diseases of the intestinal tract, like typhoid fever and cholera.”

In the demonstration of the statements made above, Walker and Sel-lards fed the different kinds of amoebae described to inmates of the Bilibid Prison. Apparently, these investigators have established a clear-cut differentiation between amoeba and entamoeba, have shown that the former is never pathogenic to man, and that the latter contains at least two species, *Entamoeba histolytica* and *Entamoeba coli*, which can be distinguished one from the other microscopically. While both are parasitic to man, only *Entamoeba histolytica* is pathogenic to man.

The most distinctive and constant differences between *Entamoeba histolytica* and *Entamoeba coli* are formulated by Craig in Table XX.

TABLE XX

DIAGNOSTIC POINTS IN THE DIFFERENTIATION OF *ENTAMOEBIA HISTOLYTICA* AND
ENTAMOEBIA COLI

VEGETATIVE OR MOTILE STAGE OF DEVELOPMENT. LIVING SPECIMENS

	ENTAMOEBIA HISTOLYTICA	ENTAMOEBIA COLI
Size.	18 to 80 microns. Average 20 to 35 microns.	15 to 50 microns. Average 20 to 30 microns.
Motility.	Very active and progressive.	Sluggish. Rarely progressive.
Cytoplasm.	Ectoplasm and endoplasm well differentiated.	Ectoplasm and endoplasm very poorly differentiated.
Pseudopodia.	Large, finger-shaped, clear and glass-like in appearance.	Shorter and blunt. Not glass-like in appearance.
Vacuoles.	Not present in most fresh living specimens.	Endoplasm filled with vacuoles.
Inclusions.	Red blood corpuscles. No bacteria, crystals or other material.	Numerous bacteria. No red blood corpuscles. Crystals.
Nucleus.	Generally invisible.	Visible.

	VEGETATIVE STAGE OF DEVELOPMENT.	STAINED PREPARATIONS
Nuclear membrane.	Delicate. Inner surface lined with single layer of minute chromatin grains.	Thicker. Inner surface lined with coarser chromatin grains.
Karyosome.	Very minute. Situated in center of nucleus.	About twice as large as in <i>histolytica</i> and situated eccentrically.
Intranuclear chromatin.	No chromatin between karyosome and nuclear membrane.	Chromatin grains between karyosome and nuclear membrane.
Cytoplasm.	Not vacuolated.	Much vacuolated.
Inclusions.	Red blood corpuscles. No bacteria or crystals.	No red blood corpuscles. Bacteria, crystals and other material.

	CYSTIC STAGE OF DEVELOPMENT. UNSTAINED OR LIVING SPECIMENS	
Size.	6 to 20 microns. Average 7 to 15 microns.	10 to 22 microns. Average 12 to 18 microns.
Shape.	Generally spherical. Rarely irregular or oval.	Almost always spherical.

	CYSTIC STAGE OF DEVELOPMENT.	STAINED PREPARATIONS
Nuclei, number	One to four.	One to eight. Sometimes more, up to 24.
Nuclei, structure	Like vegetative form but smaller. Delicate membrane, minute central karyosome, no chromatin between membrane and karyosome except the minute grains on membrane.	Like vegetative form but smaller. Thicker membrane with larger grains of chromatin, larger karyosome eccentrically placed and chromatin grains between karyosome and membrane.
Chromidial bodies	Bar, oval or rod-like masses with rounded ends. Present in about 50 per cent of the cysts.	Filamentous or spicular with square or pointed ends. Present in less than 10 per cent of the cysts.

Dobell gives the following description of this rhizopod:

"The active forms of *E. histolytica* show great variation in size, ranging from about 18 microns in diameter up to about 40 microns. As a rule, however, they measure between 20 microns and 30 microns when rounded. The living animals, when fresh and healthy, are extremely active. They flow along in a sluggish-like manner with great rapidity, and show no conspicuous differentiation between ectoplasm and endoplasm. When they have been outside the body of their host for sometime, however, at a tem-

perature lower than that of the body, they present quite different though equally characteristic movements. They then remain in one place, throwing out large, hyaline, blade-like pseudopodia composed of ectoplasm sharply separated from the endoplasm. This movement is, in my opinion, seen only in animals which are already in some degree degenerate. But it is very characteristic of this species, and serves to distinguish it from *E. coli*."

The endoplasm consists of fine granules floating in or surrounded by a homogeneous, colorless material having the appearance of ground glass. The cytoplasm is a coarsely reticulate structure, and in the stools many vacuoles may be seen; but these are degenerative forms. As found in stools, this parasite often contains red corpuscles, sometimes as many as 40 in a single animal, but usually less than 10. It is generally assumed that the presence of red corpuscles in an amoeba found in human stool is sufficient to identify it as *E. histolytica*. These corpuscles undergo digestive changes in the vacuoles and, consequently, are often fragmented. The nucleus of *E. histolytica* is usually quite indistinct. It consists of granules of fairly uniform size. It is generally stated that it contains a centriole, but Dobell, a most careful and expert investigator, is inclined to deny this. As has been pointed out, a microscopic differentiation between *E. histolytica* and *E. coli* is best made by counting the nuclei in the cysts. Encystation takes place in the intestines and when the cyst is first formed it has only one nucleus. This divides into two, and each of these into two, forming four nuclei, and the cysts found in the stool are characterized and distinguished from *E. coli* by having only four nuclei. When it has reached the quadrinucleate stage, and this occurs in the intestine, there is no further nuclear division. There is marked variation in the size of the cysts, the diameters ranging from five to twenty microns. In form, the cysts are spherical or ovoidal, though, as a rule, they are not perfectly symmetrical. More will be said upon this subject later.

Life-History.—The normal habitat of *E. histolytica* is in the intestinal wall of man. Occasionally it pierces the intestinal wall and is carried by the blood current to some other organ, where by its destructive effect upon the tissue, it causes an abscess. The most common seat of secondary infection is in the liver, which organ is reached through the portal vein. More rarely, this parasite reaches the brain, the spleen, or possibly some other organ, where it causes an abscess. It is evident, however, that the normal habitat is in the intestinal wall, and when the amoeba reaches some internal organ it does so not only to the injury of its host, but to the ultimate destruction of itself. The amoeba pours out a specific digestive secretion which acts upon the tissue of the intestinal wall. Digestion is, in part at least, carried on outside the parasite and it absorbs its food, already partially digested. Whether

intracellular digestion is essential to absorption and assimilation has not been demonstrated, but is quite properly assumed. That there is intracellular digestion of red blood corpuscles there can be no doubt. This is shown under the microscope by the fragmentation and final disappearance of these corpuscles within the animal cell. This parasite is properly named "*histolytica*," and it is quite certain that its penetration and destruction of the intestinal wall is not due to mechanical means nor to processes of intrasusception, but to a real extracorporeal digestion. It is through the action of the digestive secretions of the parasite that the characteristic intestinal lesions of amoebic dysentery are caused.

There is still room for discussion as to the relation between *E. histolytica* and certain bacteria which accompany it. Some have argued that amoebic dysentery is a result of symbiotic action of amoebae and bacteria. This idea is due to several observations. In the first place, amoebae in the intestinal tract are always associated with bacteria. In the second place, bacteria are often observed within the amoebic cell. In the third place, those amoebae which have been cultivated artificially grow best upon preparations containing bacteria. None of these, however, proves that in the production of ulcers in the intestine *E. histolytica* is in any way aided or abetted by bacteria. It has been demonstrated that in certain amoebic liver abscesses there are no bacteria, and, indeed, the only living, multiplying thing in these abscesses is the amoeba. It follows, therefore, that for the digestion and destruction of tissue, *E. histolytica* needs no bacterial help. In the second place, while it is true that bacteria are often seen in the cells of *E. histolytica*, it has not been decided whether these included bacteria are serving as food for the animal cells, or are feeding upon the cells which they have invaded. As to the growing of certain amoebae in bacterial cultures, there can be no question that at least many members of the genus *Amoeba* do feed upon bacteria, but this is no proof that *E. histolytica* uses the same food. The weight of evidence is that *E. histolytica*, unaided, causes the intestinal ulcerations characteristic of this form of dysentery.

In the ulcers the parasite is free. Here it feeds and reproduces its kind. From the ulcers some of the parasites are constantly wandering into the lumen of the gut and here some of them are encysted. This encystation is undoubtedly a protective measure. In the stools there are both free and encysted amoebae. The former speedily die. The encysted forms withstand many conditions which prove fatal to their naked comrades; in fact, encystation is undoubtedly a provision for the prolongation of the extracorporeal existence of the animal. Protected by its armor, it is no longer in need of food, it resists destruction and

other injury, and only awaits opportunity for transfer to a host. The cysts are swallowed in food or drink, and in their encysted state these organisms resist the action of the gastric juice and safely pass the portal of entry into the intestine. It has been shown experimentally that gastric juice does not dissolve the cyst enclosing *E. histolytica*. Having reached the small intestine, the cyst wall is dissolved by the trypsin of the intestinal juice, and the parasite is set free to begin again its activities in its normal habitat.

McCarrison, from both experimental studies on monkeys and clinical observations on man, is quite certain amoebic dysentery is most frequent among those who subsist on a diet deficient in vitamins and that this disease is often speedily relieved by dietetic measures. He says:

"*Entamoeba histolytica* is no doubt the specific infecting agent in amoebic dysentery, but that it can establish itself on a healthy intestinal mucosa is open to doubt. In the prevention of dysentery there are two precautions necessary: (1) The maintenance of the healthy and protective activity of the intestinal tract; and (2) the prevention of infection. The conditions necessary for the infection of the intestinal mucosa differ little from those necessary for infection of the skin; these conditions are provided by ill nourished, poisoned and imperfectly functioning tissues. Improper food supply is the most ready means of inducing such changes in the intestinal mucosa."

Multiplication.—There has been marked difference of statement concerning the methods of multiplication in this organism. Schaudinn taught that it multiplies, under certain conditions at least, by the formation of spores. This was apparently confirmed by Craig and others, but Craig no longer believes in spore formation, stating that he mistook degenerating forms of *histolytica*, which are very common in dysenteric stools, for the so-called "budding" or "sporulating" forms of the parasite described by Schaudinn. At the present time it is definitely proved that multiplication by spore formation or "budding" does not occur in this species, and that multiplication, in the vegetative stage of development occurs by direct binary fission. The nucleus increases in volume, becomes more prominent, and often of a spindle shape. The chromatin gradually collects at each end of the spindle, the distance between these collections increases, the connecting filaments become more tenuous, and finally two daughter nuclei are entirely detached and the amoeba appears with two nuclei. In the next stage, the animal elongates, divides into two practically equal portions which finally separate entirely, thus giving rise to two amoebae, each supplied with one of the daughter nuclei. Dobell describes this binary fission as follows:

"The two daughter nuclei undergo reconstruction, into the form of the resting nucleus, by gradual rearrangement of the chromatin granules on the nuclear membrane and differentiation of the karyosome in the center. The whole organism becomes elongated, and the nuclei pass to its ends. A constriction then appears in the middle of the animal and gradually deepens until complete constriction into two is effected.

Remnants of the thread which originally connected the two daughter nuclei often persist for a considerable time, as little knobs or outgrowths on the daughter nuclei."

Multiplication occurs mostly, if not altogether, in the tissue. It is best studied by killing cats infected with this organism and making sections through the intestinal ulcerations without delay. It is true that Harris reported binary fission as observed in the stool, but no one else, so far as we know, has been equally fortunate, and it requires both patience and skill to satisfactorily obtain sections of the ulcerated intestines showing these animals in a stage of fission. Multiplication goes on, for a time at least, in the abscesses formed by the invasion of the liver, brain, and other organs; in short, fission is a process which occurs at the same time and in the same place as the animal feeds.

Multiplication by sexual conjugation has been suspected by some observers, but it has not been demonstrated. On this point Craig writes as follows:

"I have several times observed a process which may be interpreted as conjugation in this species of amoeba. Two organisms may sometimes be noted lying in contact, while marked streaming of the protoplasm of each is present. It often appears as though there was an interchange of protoplasm and I am sure that at times I have seen the nucleus of one within the cytoplasm of the other. Besides the streaming motion of the protoplasm the organisms are frequently observed to apparently revolve about one another, while still attached, this movement alternating with the motion of the protoplasm. * * * It is impossible at present to be sure of the exact nature of this process, but it appears to me more than probable that it is an instance of true conjugation."

Encystation.—As we have already stated, encystation is preparatory to the exit of the parasite from the body of its host and is for protective purposes. Encystation occurs in the lumen of the intestine. It does not take place in the ulcers, nor in the abscesses, formed in cases of secondary infection. Before encystation, the parasite decreases in size. Whether this is due to fission or to the extrusion of nonessential constituents of the cell, has not been definitely determined. The preecystic organism is smaller than the average found in the dysenteric stool. Great numbers of amoebae are thrown from the body unprotected by cysts. These speedily die. Some leave the body while the process of encystation is still incomplete. These also die and there is no evidence that encystation continues to develop after expulsion from the body. The cyst wall is formed by an excretion from the parasite; in other words, it encysts itself. The cyst wall consists of a single layer and as has been stated, this is impervious to gastric juice but is readily digested by trypsin. Concerning cysts and their resistance to untoward conditions, Dobell makes the following statement:

"The cysts of *E. histolytica* will survive for several weeks outside the body of man, if they are kept moist and cool. They will live in damp feces or in water without

showing any conspicuous change save the loss of their chromatoid bodies. As a rule, if the cysts are kept under observation, it will be found that some of them remain alive much longer than the others. In water or feces some will usually be found dead at the end of a week, many more after the lapse of a fortnight, and after this period only isolated survivors will be discoverable. The longest time of survival which I have observed is five weeks (cysts kept in water), but as a rule they will not live so long. Desiccation kills them immediately, and they degenerate much more rapidly at a high than at a low temperature. At body temperature they generally die within a few days at most. Degeneration of the cysts is readily recognizable. The nuclei first become unnaturally distinct in the fresh cysts—owing to the coagulation which occurs on the death of the protoplasm—and then break up. As the cysts die they also, become permeable to aqueous solutions of various stains (eosin, etc.). The cytoplasm becomes vacuolated, and finally disintegrates. Cysts are passed in the feces in the uninucleate, binucleate, or quadrinucleate stage. Those containing less than four nuclei never develop to maturity outside the body, and usually die much sooner than the mature cysts. Even cysts with dividing nuclei do not complete their nuclear divisions. Spindle-figures and other stages arrested in division can be seen to remain unchanged within the cysts until degeneration takes place.”

When the cysts are fed to cats a large percentage of these animals—sometimes ninety—develop dysentery, usually within from seven to nine days. Walker fed 20 men on encysted *Entamoeba histolytica*. He succeeded in infecting 18 out of the 20, as determined by the appearance of the cysts in the stools, the time required for this varying from one to 44 days and averaging about nine days. Although 18 men were infected, as shown by the presence of the amoebae in their stools, only four developed dysentery and in two of these the clinical symptoms were mild.

Pathogenicity.—There has been considerable discussion as to the existence of strains of *E. histolytica* of variable virulence. This has been offered as an explanation of the well-known fact that many men carry this organism in their intestines and are constantly eliminating it in their stools without manifesting any symptoms of the disease. It is supposed that these men have been infected with a mild strain, while those who develop the symptoms and lesions are supposed to have swallowed more virulent strains. It is more than likely that the difference in susceptibility lies in the host rather than in the parasite. It must be evident that, for both guest and host, it is desirable that they live in harmony. In most men the parasite, although feeding on the intestinal wall, destroys so small a part of this tissue in order to support its life, that no recognizable injury comes to the man. In this way, carriers of amoebic dysentery in certain sections of the country are numerous and most of those who contract the disease obtain the parasite not from one who is sick, but from a healthy carrier. Walker divides those who are eliminating pathogenic amoebae in their stools without at the time showing any ill effects, into two classes, contact carriers and conva-

lescent carriers. The former are those who are never sufficiently affected by the location and activity of the parasite in their intestines to recognize its presence. These contact carriers are numerous in certain localities. The convalescent carrier is one who has had the disease and has, in part at least, recovered from it. He also goes about among his fellow-men and infects localities.

It is worthy of note that as a result of recent studies, Kofoid and his students conclude that amoebae cause certain forms of arthritis and play an important rôle in the development of Hodgkin's disease.

Entamoeba Coli.—We have already pointed out the similarities and the differences between *Entamoeba histolytica* and *Entamoeba coli*. At this place, we simply desire to emphasize the fact that *Entamoeba coli*, while parasitic to man, is without pathogenic properties. Finding entamoebae in the stools is not sufficient to make a diagnosis either of amoebic infection or amoebic disease.

Entamoeba Gingivalis.—This is an organism which is found in the mouth, especially in the tartar which forms on the teeth. Some interest was awakened in it a few years ago by the claim made by Bass and others that it is a cause of pyorrhea. This claim has not been sustained and, so far as we know at the present time, this organism is entirely harmless.

Endolimax Nana.—This is a small amoeba occurring in the human intestine, nonpathogenic in character, but important from a diagnostic standpoint, because it forms four nucleated cysts which may be mistaken for the cysts of *Entamoeba histolytica*, the cause of amoebic dysentery. These cysts are differentiated from those of *Entamoeba histolytica* by their smaller size, oval or irregular shape, the morphology of the nuclei, and the absence of the distinctive chromidial bodies so frequently observed in the cysts of *histolytica*.

Other Animal Parasites Which May Cause Dysentery.—In 1857 Malmsten studied and described a large ciliated monad which he found quite constantly in the intestines of pigs. This animal is from 0.06 to 0.1 mm. in length by 0.05 to 0.07 mm. in breadth. It is covered with parallel rows of cilia. It has a kidney-shaped nucleus and multiplies both asexually by fission and by conjugation. It is, in part at least, eliminated from the intestine of the pig in an encysted form. If these cysts are swallowed by man the organism is liberated in his intestine and may cause ulceration of the rectum. This condition is known as balantidic dysentery. Malmsten discovered this organism in the stools in a case of diarrhea with ulcer of the rectum. Casagrandi and Barbagallo fed cats upon the encysted form of this parasite and produced in these animals enterocolitis. Balantidic dysentery, while not common, is occasionally seen in the tropics and has been studied quite thoroughly in the Philip-

pinus by Strong. The disease comes on insidiously with alternating constipation and diarrhea, with the occasional passage of mucus and blood. In some instances, the emaciation is accompanied by marked edema of the face and limbs. Recently (1920) Nisbet reported a case of this disease in a farmer residing in North Carolina. This man had long suffered with intermittent attacks of diarrhea with occasional discharge of blood and mucus in his stools. Examination of the sigmoid showed numerous ulcers from 5 mm. to 5 cm. in diameter. The stools contained numerous balantidia. In the discussion of Nisbet's paper, Eastland, of Texas, reported that he had seen 30 cases of balantidic dysentery in his practice during the past 18 months, and he stated that the chances of detecting this parasite are increased if one examines the second stool passed after purgation. Simon, of New Orleans, does not believe that this form of dysentery is so prevalent in this country and states that the total number of published cases in the world is 175.

In 1904 Strong collected from the literature 127 cases of balantidic dysentery, with 35 deaths. In 32 of the fatal cases, autopsies were made, 28 showing an ulcerative colitis and four a chronic catarrhal colitis. Walker infected monkeys with balantidia and came to the following conclusions: (1) Parasitization with balantidia is relatively common in the Philippine Islands. (2) A large proportion of the pigs in and about Manila carry balantidium. (3) Morphologically, balantidium suis is identical with balantidia hominis. (4) Balantidium is the primary etiology factor in balantidic dysentery. In 1917, Manlove, in Manila, autopsied two cases of balantidiasis. In one there was a history of dysentery, while in the other the intestinal condition was unimportant and was discovered in a routine examination. This author concludes that balantidiasis is relatively unimportant as a cause of death in the Philippines, but may cause considerable morbidity.

There are several varieties of balantidium, as *B. minutum*, *B. italicum*, and *B. japonicum*, all of which are said to be capable of causing dysentery in man. This is true of certain related genera, such as *Colpoda cucullus*, *Nyctotherus faba*, *N. giganteus*, and *N. africanus*. The larvae of certain diptera frequently cause dysenteric diseases in some of the lower animals, especially the horse, and are believed to be rare causes of similar diseases in man. Under the name Laveranic dysentery, Castellani describes a disease which is accompanied with high fever, great distress, marked prostration and the passage of stools containing blood and mucus. This disease accompanies certain severe forms of tropical malaria and it may be said in this connection that at one time it was believed that malaria and dysentery are closely related; in fact, dysentery was often believed to be a malarial disease. This opinion

apparently prevailed largely among medical officers during the War of the Rebellion. It cannot be denied that malaria and dysentery are often prevalent at the same time and in the same neighborhood, and it must be admitted that the two diseases often coexist in the same individual, but we see no reason for concluding that there is a specific malarial dysentery. More than 70 years ago, Cordier wrote that the theory of the malarial nature of dysentery was founded upon error in the statements of facts and was the consequence of a false theory put forth and defended with unjustifiable and unwarranted obstinacy. On this point Hirsch wrote in 1886 as follows:

“Throughout that large *area of distribution*, dysentery and diarrhea exhibit an almost complete correspondence with the malarial diseases in respect to the manner of their endemic prevalence, the frequency of their epidemic outbreaks, and the varying severity of their type. Like the malarial diseases they reach the maximum of diffusion and of intensity, and more especially their greatest severity as an endemic, in equatorial latitudes; in subtropical countries there begins to be noticed a decrease in the extent and seriousness of their endemic and epidemic incidence, while in still higher latitudes they almost disappear as endemic diseases and show themselves merely now and then in epidemics over an area at one time large and another time small. In one point they differ from malarial diseases, namely, that they attain to higher latitudes of the cold zone, appearing as epidemics in regions that are quite free from malaria.”

Castellani found in two cases of dysentery, apparently contracted in Burma, peculiar protozoal bodies, while amoebae and dysentery bacilli were present. The organisms observed consisted of elongated or oval bodies, one end of which seemed to be constantly vibrating. This led the observer to suspect the presence of flagella or cilia or an undulating membrane. This parasite does not protrude pseudopodia, but changes in shape are frequently taking place. On insufficient evidence, as it appears to us, Castellani believes this organism to be the cause of dysentery in these cases. He calls this entoplasmic dysentery. Under the name leishmanic dysentery, Castellani and Chalmers describe a dysenteric form of kala-azar. Their diagnosis was based on the presence of leishmanic bodies in the spleen or liver and on the absence of amoebae and dysentery bacilli in the stools. These authors admit that amoebic and bacterial dysentery are not rare complications in kala-azar.

Under the head of platyhelminthic dysenteries, Castellani and Chalmers mention forms of dysentery which they believe to be caused by *Fasciolopsis buski*, *Schistosoma japonicum*, and *S. mansoni*. In these cases, the eggs of the parasite may be found in the stools.

Recently (1921) Sweet has reported the wide prevalence of fasciolopsis as an intestinal infection in Shaohsing, China. In the examination of 732 stools from hospital and dispensary patients he found this parasite in 71.5 per cent. He states that the infestation usually is ac-

accompanied by a diarrhea without blood. In chronic cases there may be edema of the face and hands, while in a slightly smaller percentage the abdomen becomes enlarged and pendulous. The ova are easily found in the stools and examination of the blood shows a moderate eosinophilia.

The same authors, under the head of nemathelminthic dysenteries, include certain diseases in which immature females of the genus *Oesophagostomum brumpti* have been found. One such case has been reported from West Africa and another from South America.

Spirochetic Dysentery.—This was first reported by Le Dantec. The finding of this author, however, has not been confirmed, and consequently his report has not been accepted. More recently, Castellani has reported a dysentery which he ascribes to a polymorphic vibrio. At times this organism appears as a coccus; again as a large spirochetal body, and more frequently as a vibrio varying greatly in size. It is highly motile, does not ferment lactose, grows readily on the usual laboratory media, and in liquid cultures forms a characteristic pellicle. It produces neither acid nor gas on media containing the usual carbohydrates, but often produces a marked alkalinity in the culture medium. This is not the first time that similar organisms have been reported in connection with various diseases. They are characterized by their great variety in shape, size, and by the production of alkali. The investigation of these organisms promises a rich field for research.

The Bacillary Dysenteries

History.—After the causal relationship between certain amoebae and dysentery had been well established, it was shown that in many localities where dysentery is endemic or epidemic no amoebae can be found in the stools during life or in the body after death. This was convincing proof that all dysenteries are not of amoebic origin and search for bacteria which may play a part in the causation of the dysenteries was prosecuted. Escherich quite convinced himself that the colon bacillus may take on unusual virulence even in its normal habitat, the intestines of man, and manifest its effects by causing ulceration. Celli described a bacillus belonging to the colon group, which ferments glucose and clots milk and he named this organism *Bacillus coli dysentericus*. This may have been one of the now well-recognized dysenteric bacilli. Calmette was quite convinced that in Cochin China dysentery may be caused by the *Bacillus pyocyaneus*. This announcement met with apparent confirmation by the studies of Lartigan in the United States, Adami in Canada, and others, but it is now generally believed that this is in error.

In 1898 Shiga showed that amoebae are not found in the severe epi-

demics of dysentery prevalent in Japan, but he did find in the stools during life and in the body after death a well-defined and easily recognized bacillus. Since he found this organism in all his cases and since its cultures were agglutinated by high dilutions of the blood serum of those ill with this disease, Shiga felt justified in claiming that he had found the specific cause, and subsequent studies have confirmed this claim. This organism is now generally known as the Shiga bacillus.

Two years later (1900) Flexner, in a report of an expedition to investigate the diseases prevalent in the Philippines, described a bacillus found in epidemics on these Islands. It also was present in all cases and agglutinated with dilutions of the blood serum of the sick. There was for a time much discussion about the identity of these two organisms. It would be profitless to follow these discussions, since it is now generally assumed that the differences are sufficient to justify the conclusion that it is a different species, and this is now known as the Flexner bacillus. There are two other bacilli capable of causing dysentery. These are varieties of the Flexner bacillus. One is known as the His-Russell and the other as the Strong bacillus.

The Shiga Bacillus.—This is a small plump rod with rounded ends. It was at first believed to be motile, but closer studies showed that it has no flagella and no active motion, although it demonstrates the Brownian movements in a marked degree. It is sporeless and ordinarily it needs frequent transplantation in order to keep it alive. However, according to Martini, if an agar culture tube be hermetically sealed, the rods disintegrate into a granular debris which is not easily stained and shows no rods. If this granular mass, even after a year, be placed in fresh medium, normal rods develop. This observation has been confirmed by similar findings with the plague bacillus and it deserves to be studied more closely and thoroughly. Fresh cultures have a sperm-like odor, while older ones develop trimethyl and ammonia. Very old growths have a strong and penetrating fecal smell. It takes the ordinary stains easily, but the staining is not always uniform; sometimes it is polar. The bacillus develops on ordinary media without any characteristic exhibitions. Culturally it is distinguished from the Flexner and related dysentery bacilli by the fact that it develops no acid when grown on media containing mannite, maltose, or saccharose. The Shiga bacillus is furthermore distinguished from the other organisms of this group by the development of a soluble toxin. This will be discussed more in detail later.

The Shiga bacillus is not highly resistant to unfavorable conditions. It is easily destroyed by the usually employed disinfectants, both the soluble and the gaseous forms. However, it retains both viability and virulence for days when deposited on clothing or food. It soon dies out

in running water and epidemics of bacillary dysentery due to infected water are probably rare. In sterilized water it lives for many weeks, but in the presence of the usual saprophytic bacteria of water it soon dies.

The Flexner Bacillus.—Morphologically, culturally, and tinctorially, this organism differs but little from the Shiga bacillus. It, however, produces indol in pepton cultures more abundantly; produces acid in mannite cultures; rapidly reduces nitrates to nitrites, and elaborates a soluble toxin either not at all or only in small amount. These differences in function rather than in form, led to the conclusion that the two organisms are of different species. The His-Russell is a variety or strain of the Flexner bacillus. It produces indol more slowly, reduces nitrates less energetically, and decomposes mannite, but is without action on maltose and saccharose. The Strong organism is even more closely related to the Flexner bacillus and, in fact, there seems to be no constant differences when many strains of both are studied. The Shiga bacillus, with its subvarieties, is now known as the dysentery bacillus rich in toxin production, and the others as poor in this product. The latter are found to be more stabile. They are not so easily overgrown by saprophytic bacteria; they retain their vitality for a long time under adverse conditions, and they are not so easily destroyed by disinfectants. They may persist for many days in drinking water, for many weeks on clothing, and cultures need to be transplanted only every second or third month.

Pathogenicity.—Rabbits, mice, dogs, goats, and horses are highly susceptible to subcutaneous, intraabdominal, and intravenous inoculations with these bacilli, especially the Shiga bacillus. Very minute doses introduced by these avenues cause acute fever, with paralytic symptoms, in the extremities, dysenteric stools with mucus and blood, then a rapidly falling temperature ending in death. Autopsy shows an inflammatory condition of the kidneys, lungs, and the mucous membrane of the intestinal tract. The bacilli are found in these cases in the stools, in the blood, and in the various organs. With still smaller doses the disease is more chronic and the lesions are more advanced with neerosis of the intestinal epithelium and ulceration in the large intestine. These effects are produced by both living and dead bacilli of the Shiga type; also with filtered cultures. This shows that the nature of the process is an intoxication rather than a pure infection. Even one one-hundredth of a loop of a culture may induce these symptoms and lesions in mice. Strange to say, the guinea pig is relatively resistant to this organism. From the researches of Gay, we learn that the horse shows marked ele-

vation of temperature, with prostration and labored breathing when treated with one-fourth the minimum fatal dose for guinea pigs.

There has been much controversy concerning the nature of the soluble toxin found in cultures of the Shiga bacillus. Some claim that it is a true toxin, a secretion of the bacillary cells, while others contend that it is an autolytic product, resulting from the cleavage of the bacilli. Antitoxic sera in variety have been made and have been used for both prevention and cure. Living and dead cultures have been used in the preparation of the toxins and, as happens when bacterial cell substance is repeatedly injected, many animals die in the process of immunization. There is no standard method of preparing the antitoxin as there is for diphtheria. It follows that the antitoxic sera are not of uniform value and there is still some doubt as to whether their effects should be ascribed to bactericidal or antitoxic properties. Gay has obtained a serum by treating horses with Flexner's bacillus, and has treated cases of dysentery with this with good results, but Escherich, in Vienna, did not find it so valuable. Numerous observers have reported great reduction in the mortality in cases of Shiga infection by treatment with the specific antitoxin.

All attempts to induce typical dysentery in ordinary laboratory animals by feeding with dysenteric bacilli have failed. It is true that massive doses may cause some intestinal inflammation with loose stools, but many bacteria will bring about this result. In apes the disease may be induced by feeding, and it is stated that dysentery is sometimes epidemic among these animals. This is certainly true of apes in captivity, one such epidemic having been observed in Paris and another in Manila. Subcutaneous injections of dead bacilli in man have been used for vaccination purposes, but quite naturally, the value of such a procedure must remain undetermined until it has been done on a large number of persons living in the midst of epidemic dysentery. Lüdke vaccinated himself in this way, but later became infected while working with living cultures. He, therefore, concludes that if subcutaneous injections of dead cultures have any protective value, it is of short duration. In a local epidemic in an insane asylum Fuksch vaccinated the men and left the women without treatment, and states that the disease did not spread further among the former while it continued among the latter. Shiga (1898-1900) vaccinated 10,000 Japanese in localities in which dysentery was prevalent and found that this procedure did not reduce morbidity but had a marked and gratifying effect on the mortality. In some localities, while the death rate among the unvaccinated reached from thirty to forty per cent, there were no deaths among the vaccinated. The same investigator vaccinated large numbers of the Japanese troops in the war with Russia. At this time he suspended dead

bacilli in antitoxic serum and made three injections at intervals of three or four days, increasing the size of the dose at each injection.

Castellani and Chalmers make the following statement concerning the pathogenicity of dysenteric bacilli:

“The bacilli taken into the body with food and drink pass to the intestine, in which they grow and multiply, and along the whole length of which they can be found. The researches of Flexner and Sweet have proved that the bacilli can abound in the small intestine, where no pathological lesion may be found. In the bowel they give rise to the toxins, of which two are known—one which acts upon the lower bowel, and the other on the nervous system. Both these toxins are absorbed into the blood, but the first, being excreted by the large bowel, causes the lesions well known to be associated with dysentery, and explains the localization of these lesions. In the process of excretion this toxin first causes an exudation of lymph into the submucosa, and later into the mucosa. This lymph coagulates and is invaded by a cellular exudate, and in due course the glands and the tissue of the mucosa and the muscularis mucosae are destroyed by coagulative necrosis, with thrombosis of the vessels. This fibrinous or diphtheroid membrane is at first most marked on the summits of the ridges, and may not be found at the bottom between the ridges. It contains large numbers of micro-organisms of varying characters, while the depths of the submucosa may reveal accumulations of leucocytes, and the peritoneal coat may be edematous. The micro-organisms destroy the fibrinous false membrane, which may separate off in flakes, thus causing ulcers, which are at first superficial, but later become deep and extensive. After treatment these ulcers heal with the formation of connective tissue, thus producing a scar in the mucous membrane, which in due course becomes pigmented from the sulphuretted hydrogen of the bowel acting on the iron of the blood. The other toxin may attack the nervous system, causing peripheral neuritis. Very rarely do the bacilli enter the blood stream, and cause true septicemia, though such cases have been recorded by Rosenthal and Markwald, the latter observer stating that he found the bacilli in the blood and intestinal contents of a fetus which had been prematurely expelled from the uterus of a mother who was suffering from bacillary dysentery. Darling has actually grown the bacillus from the blood of cases of bacterial dysentery. Occasionally bacilli affect the joints and very rarely the conjunctiva.”

There can be no doubt concerning the causal relation of these bacilli to dysentery in man. As has been stated, high dilutions of the blood of those sick agglutinate cultures of these bacilli. This is positive, but not conclusive, evidence. There is, however, confirmatory proof. Strong fed pure cultures of the Shiga bacillus to two criminals sentenced to death and both developed typical dysentery. Jehle drank mixed Shiga and Flexner cultures and developed the disease on the third day. He found both bacilli in his stools. Several accidental laboratory infections have occurred. Each of these bacilli produces typical dysentery with characteristic symptoms and lesions. The Shiga is the more virulent, but otherwise the results are the same. Close study shows that the varieties of these bacilli might be multiplied, but, while this is of scientific interest, it is not of great practical importance. These bacilli are dis-

tributed all over the world, having been found in all climes and among all conditions of men.

Sources of Infection.—Like typhoid fever, dysentery is always due to the transfer of the excreta of one person to the ingesta of another. In the great majority of instances infection is transferred through contact, which may be direct or indirect. The prevalence of dysentery is determined by the extent to which fecal contamination exists in the locality. The disease is most abundant where fecal disposition is most primitive. With improvement in the latter, the disease grows less. Thirty years and more ago dysentery, under various names, such as “mucous and bloody diarrhea” and “bloody flux,” reaped rich harvests, especially among children, in various sections of this country. As methods for the disposal of fecal matter grew more efficient the death rate from this disease decreased. It decreased at first in cities with the introduction of water-closets, then it grew less in villages in which the same improvement was inaugurated, and lastly, its highest prevalence was in the less progressive and more ignorant communities. Its dependence on ignorance and filth for its dissemination is shown by the frequency of outbreaks in insane asylums, and especially in wards occupied by those who pollute themselves, their clothing and bedding, and even smear the walls of their rooms with fecal matter. In primitive places there are not even privy vaults; stools are deposited at random on the ground; everything about the individual home and throughout the village becomes soiled with fecal matter. These are the localities in which dysentery most abundantly flourishes. With typhoid fever, it has spread through camps and decimated armies. It has accompanied military and civil explorations even into uninhabited regions and has flourished wherever man has found even a temporary abiding place and has surrounded and befouled himself with his own excretions. This does not mean that it may originate *de novo*, for it does not; but the sick and the well may long harbor the bacilli in their intestines and plant them over wide regions in their stools. Hands, the person, clothing, bedding, food, and water may bear the infection. From the dirty hands of the milker, the cook, or the waiter, these organisms may find their way into the food. Those recovering from the disease may continue for weeks as veritable culture flasks for the growth and distribution of this virus. Others may carry the bacilli without developing the disease. Flies, and possibly other insects, aid in its distribution. While the bacilli are not spontaneously generated in filth, they are widely disseminated and they flourish in polluted places. An epidemic of amoebic dysentery, undoubtedly transmitted by flies, was studied by Craig in 1917. It occurred among the United States troops stationed at El Paso, Tex., and 156 cases of the dis-

ease occurred before the epidemic was controlled. Very careful epidemiologic studies were made of this outbreak and the only logical conclusion that could be drawn from the evidence was that the infection was almost entirely transmitted by the flies which swarmed in the camps at the time the epidemic occurred.

Contact Infection.—Numerous small epidemics of dysentery, both amoebic and bacillary, have been recorded. An instance of this kind in which the cook was infected, is reported by Bussov, of Graz. The patients in a hospital whose food was prepared by this infected cook developed a bacillary dysentery, while other patients in the same hospital with whom this cook did not come into contact in any way, escaped. A local epidemic confined to one block in Charlotte, N. C., is reported by Allan. The latter observer states that the death rate in amoebiasis in Charlotte constantly exceeds that from typhoid fever. He also calls attention to the fact that amoebae are often found in the stools of pellagrins. We are inclined to the opinion, however, that Allen diagnosed every case in which he found amoebae in the stools as amoebiasis, and we know that this is not justified unless the kind of amoebae found is identified.

The Flagellate Diarrheas

Discussion.—In the group of the Mastigophora there are three flagellates which are frequently found in the intestines of man. These are *Lamblia intestinalis*, *Trichomonas intestinalis*, and *Tetramitus mesnili*. *L. intestinalis* has not been found in the encysted form. It leaves the bowels in the free or vegetative state. Its natural habitat is the large intestine and cecum, where it grows in enormous numbers and in pear-shaped form, varying in length from 5 to 15 microns. The anterior end is blunt and there arise therefrom three slightly spiral flagella. At the same end there is a nucleus showing a slight conical depression. In the fresh state these organisms move rapidly by vigorous activity of the anterior flagella, aided undoubtedly by the undulations of the membrane. Under the microscope they often move so rapidly that the study of individual organisms is difficult. When seen *en masse* it is often difficult to recognize the flagella, as they seem to become attached to or wrapped up in the undulating membranes. A dark ground condenser is of aid in these examinations. It is important to note the three anterior flagella, because the number distinguishes this organism from two others closely related, the tetratrichomonas, which has four anterior flagella, and the pentatrichomonas, which has five. The trichomonas survive in the feces for many days and are quite highly resistant to untoward conditions. They withstand the action of gastric juice and when swallowed

pass into the intestines where they multiply and in some instances induce disease. This parasite is very common in rats, mice, and fowls, and is found less frequently in dogs.

In South America, Escomel has found this flagellate in drinking water, has cultivated it from diarrheal stools, and has infected dogs with these cultures. In 1912 Smithies in Chicago found trichomonas in the gastric contents of two cases.

"Both patients were women who had resided in semi-tropical climates; both had been weakened by illness and loss of blood incident to surgical procedures; both patients had habitually partaken of unboiled water from surface wells and had doubtless also eaten freely of fresh, moist, green vegetables and fruit in all probability contaminated. Neither patient had experienced periodic or chronic diarrhea; on the contrary, obstinate constipation was present in spite of the existence of enormous numbers of flagellate protozoa and motile and nonmotile bacteria in the intestinal tract. This is somewhat unusual where trichomonads are present, but the condition has also been observed by Freund and others. In each case, gastrointestinal symptoms were prominent. These were nausea, flatulence, abdominal distention, colicky pains, and constipation. Skatol and indol were present in the stools and so called 'intoxication symptoms,' as headaches, neuralgia, and exhaustion were observed. The blood showed slight anemia, with increase in eosinophils and degenerated leucocytes."

Lynch, of Charleston, S. C., has reported a case of trichomoniasis of the intestine and has inoculated rabbits with the organism. He states his conclusions as follows:

"(1) *Trichomonas* is a definitely pathogenic microorganism. (2) The intestinal form produces a mild enteritis manifested by an intermittent diarrhea. (3) Infection by this organism may occur by mouth or by rectum, more naturally by mouth, from active forms in rabbits, but probably from encysted cells in human beings. (4) The duration of the infectivity of water containing either active trichomonads or the encysted is probably not long. (5) The form of the cell may be so altered by environment as to render immediate recognition difficult. (6) This organism is capable of artificial cultivation, this having been accomplished. (7) It multiplies by direct cell division, this with the transformation into encysted form which may again become active, constituting the life-cycle of the organism. (8) Rabbits are susceptible to experimental infection by trichomonas."

The fact that Lynch reports an encysted form of this parasite while all other investigators have failed to find cysts, renders confirmation of his statements desirable.

Lambia intestinalis is of common occurrence in the human intestine and it differs from other protozoa, whose habitat is the same region, in the fact that it lives and grows most abundantly in the upper part of the small intestine. It has the shape of a split pear, with a flat surface on which there is a sucking disc, and a convex surface. The tapering end or the tail terminates in two flagella. There are three pairs of flagella located on the surface of the parasite. All of these originate in a rod-like structure occupying a central position in the animal. This proto-

zoan moves rapidly, with the swaying motion, reminding one of a flat fish in a tank of water. The lamblia varies in length from 12 to 18 microns, and on account of its characteristic shape there is no trouble in recognizing it in the stools. The vegetative form when cast out in the stools soon dies and the continuance of the life of the animal depends upon encystation, which occurs in the intestine. When the cysts are swallowed they resist the gastric juice, pass into the small intestine where the cyst wall is dissolved and multiplication of the parasite takes place. The cysts are often found in very large numbers, together with free living flagellates, in the stools of infected persons. The cysts are quite characteristic and under a $\frac{1}{12}$ inch oil immersion show from two to four nuclei. In regard to infection with this organism Wenyon says:

"*Lamblia intestinalis* is a very persistent flagellate. I have had under observation two or three persons who have maintained their infection for years. One of these has an enormous infection and sometimes passes cysts in such numbers that as many as a dozen or more can be seen in a field of the $\frac{1}{12}$ inch objective. Many attempts have been made to get rid of this infection without result, but during the whole of this time there have been no signs of intestinal derangement. In other cases there occur at intervals attacks of diarrhea with the passage of mucus in which lamblia are to be found in enormous numbers, so much so that the whole microscopic field is packed with them. After recovery from such an attack the stools become normal again and only encysted forms are to be found. The occurrence of repeated attacks of this nature with a certain degree of abdominal uneasiness preceding the attacks and the passage of such extraordinary numbers of flagellates especially in the mucus, leads me to suspect that sometimes, at any rate, *Lamblia intestinalis* may produce sufficient irritation of the small intestine to justify us in regarding it as pathogenic. The invasion of the glands of the small intestine as seen in the rabbit is suggestive of such a pathogenic rôle."

In a study of 136 consecutive cases of dysentery invalided to England from the Gallipoli battle fields, Kennedy and Rosewarne found 12 whose condition was dependent upon infection with *Lamblia intestinalis*. These authors say:

"The pathogenicity of *Lamblia intestinalis* is a question which is still not beyond the regions of doubt, hence it is only by the detailed study of series of cases like the present that the matter can be finally settled one way or the other. Within recent years several observers have recorded cases apparently of lamblia infection giving rise to a chronic dysenteric condition which resisted all the usual methods of treatment. Wenyon has had under observation two or three persons who have maintained their infection for years. Some showed repeated attacks of diarrhea with passage of mucus, and one case, although passing lamblia in large numbers, showed no signs of intestinal derangement. The persistence of the infection is well illustrated in our series. * * * The length of time during which encysted forms of *Lamblia intestinalis* were excreted is a very important point, for if the organism be pathogenic, then the question of dealing with carriers will naturally come up for solution. That they are by no means uncommon is shown by the frequency in our series—12 cases out of a consecutive series of 136 so-called dysenteries, which is approximately nine per cent. Stitt recognizes the prevalence of this infection in the tropics, and holds that it is only less important than that of amoebic dysentery."

In another series of 1,305 patients with dysentery invalided home from Gallipoli, Fantham and Porter found 187 cases of pure lambliasis. These investigators made numerous animal experimentations and state their conclusions as follows:

“(1) *Lamblia intestinalis* is pathogenic to man and is capable of producing diarrhea, which may be persistent or recurrent. (2) The virulence of the parasite varies, and lambliasis occurs in tropical and nontropical countries. The lamblia cysts can remain infective for some time. (3) Lambliasis occurs in rodents, especially rats and mice, and can be of human origin. The influence of rats and mice in the spread of lambliasis has been noted recently by Noc and by Mathis. Lambliasis may also be produced in cats. Lambliasis may be conveyed to man from these mammals. (4) As a result, rodents may be reservoirs of lambliasis, and on the Western Front this should be remembered, as we have already published.”

Haughwout has reviewed the literature of the pathogenicity of the flagellate and ciliate protozoa and has indulged in some theorizing concerning the problems involved, but has made no important contribution in the matter.

In 1902 Stiles exhibited to the Medical Society of Washington, D. C., a guinea pig which had been infected with lamblia obtained, according to Stiles, from the first case of the presence of this parasite in man diagnosed in the United States. The parasite was obtained from the stools of a child sick in Baltimore and the encysted specimens were fed to the animal. In presenting this case Stiles stated that he was not sure of the pathogenicity of the organism, but he thought it possible that heavy infections were not without harm.

Tetramitus mesnili was discovered by Wenyon in the routine examination of a man who had arrived in London from the Bahamas. This man had no intestinal symptoms and in this case the parasite is not supposed to have had anything to do with the disease from which the patient was suffering and which was confined to the chest. Since that time *Tetramitus mesnili* has been found to be widely distributed in tropical and subtropical countries and many small epidemics of diarrhea have been attributed to this flagellate. In general shape, size, and in the presence of three anterior flagella it resembles *Trichomonas intestinalis*, but it has no undulating membrane and encysted forms are usually abundant in the stools. The vegetative form, unlike that of *trichomonas*, is very short-lived and encystation seems to be essential to prolonged extracorporeal existence.

Rhamy and Metts state that during the past 17 years they have been observing occasional cases of acute or chronic diarrhea in which flagellates appear to be the only parasites present in the stools. They say:

“These parasites live best in neutral or slightly alkaline mediums, and for this reason any tissue of low vitality may harbor them. As their mode of entrance is by

the mouth, however, the gastrointestinal tract is their usual habitat. The fact that they have been found elsewhere, in our opinion does not argue against their capacity for assuming primary pathogenic roles in the bowel, and to support this view we present some selected cases of dysenteric diarrhea in which the sole cause, so far as could be found, was the flagellate protozoa, and in which most of the patients recovered under the recognized treatment for parasitic dysentery. Whatever their conclusions regarding the pathogenicity of these parasites, most observers give practically the same clinical history: The drinking of impure water followed in a few days by diarrhea with colicky pains, watery or slimy blood stained stools, weakness, dyspnea, loss of weight and progressive anemia simulating pernicious anemia. The skin becomes yellow, with a tendency to urticarial or pellagroid eruptions. The stools contain much mucus, pus, blood and active trichomonads. The blood shows a moderate eosinophilia, from six to twelve per cent. The large bowel shows superficial ulcers, the mucous membrane presenting a moth eaten appearance with here and there a diphtheritic exudate. Death may ensue, necropsy showing a cloudy swelling or fatty degeneration of heart, liver and kidneys.''

Coccidiosis

Discussion.—Coccidiosis is a disease very frequent among the lower animals. In poultry it causes a severe diarrhea which often terminates fatally and the disease spreads through these animals with epidemic violence causing great loss. The special species of coccidia known to infect birds is designated as *Eimeria avium*. This parasite is eliminated with the feces partly in encysted form, and these cysts when taken into the alimentary canal of other animals withstand the action of the gastric juice but are dissolved in the intestinal juices and cause the infection. Every one who has made autopsies on rabbits is well acquainted with the whitish nodules so frequently found in the livers of these animals. These nodules consist of coccidia, some of which are encysted while others are in the free state. Coccidia are divided into many different genera and species, the differentiation being for the most part founded upon the number of spores and the number of sporozoites which develop from the cyst.

Coccidiosis is apparently a very rare infection in man, although in some localities this does not seem to be true. During the World War, Castellani and others found coccidiosis, comparatively speaking, a common disease in the Balkans. The same observer saw six cases in Macedonia, in two of which there was diarrhea while the others did not show any intestinal symptom. Richards reported 14 cases from the Forty-Third General Hospital at Salonika. Savage and Young found six cases of coccidial infection, but in these this parasite seems secondary to the amoebae. In 1,305 British soldiers from Flanders and Gallipoli, Pantham found four cases with coccidia in the stools. It is believed by some that eating infected livers of rabbits may cause coccidial infection in man.

U. S. Mortality Statistics of Diarrhea and Dysentery.—In the mortality reports of this country one will find many deaths charged each year to dysentery and to diarrhea. Thus in the registration area in 1919 there are records of 3,732 of the former and 47,044 of the latter. Most diarrhea deaths occur under two years of age, 37,635 of the above number being under, and 9,409 over two. There is some question as to the accuracy of these causes. True amoebic and bacillary dysentery are relatively rare in this country. Dublin, from his experience in the Metropolitan Life Insurance Company, states a prevailing belief that a large proportion of the "dysentery" (so reported) is really enteritis or gastroenteritis. About one-third of the total dysentery deaths are in children under two years of age and these are most probably diarrhea rather than dysentery. The death rates charged to dysentery in the U. S. Registration Area from 1900 to 1919 are shown in Table XXI.

TABLE XXI

ANNUAL RATE PER 100,000		ANNUAL RATE PER 100,000	
YEAR	RATE	YEAR	RATE
1900	11.3	1910	6.4
1901	10.6	1911	5.2
1902	10.0	1912	4.4
1903	7.3	1913	5.1
1904	7.7	1914	4.6
1905	7.6	1915	3.8
1906	8.0	1916	5.0
1907	6.5	1917	6.1
1908	6.3	1918	5.8
1909	5.6	1919	4.4

Whether this decline is significant or whether it is due to a change in diagnosis or classification is not entirely clear. The relative reductions in the three alimentary infections—typhoid, dysentery and diarrhea—are shown in Table XXII.

TABLE XXII

U. S. REGISTRATION AREA						
ANNUAL RATE PER 100,000			RATIO TAKING RATE IN 1900 AS 100			
TYPHOID FEVER	DYSENTERY	DIARRHEA	TYPHOID FEVER	DYSENTERY	DIARRHEA	
1900	35.9	11.3	133.2	100	100	100
1919	9.2	4.4	55.3	26	39	42

Typhoid fever in 1919 is 26 per cent of what it was in 1900, dysentery 39 per cent and diarrhea 42 per cent. Whatever the cause of the latter two, it is evident that the improvement in water and milk supplies and in sanitation generally has effected a more marked reduction in typhoid than in the other two.

Deaths from dysentery have always been reported in greater numbers from the rural districts than from the cities (over 8000 population up to 1909, over 10,000 since). Thus in 1900 the rate for cities in the registration states was 9.4, for rural districts 15.1. In 1905 the respective rates were 6.4 and 10.8, in 1909, 4.1 and 7.6, in 1917, 2.3 and 9.2. The increase of the rural rate in 1917 is due to the addition of southern states to the Registration Area, where the rates are much higher. Geographical differences in rates in 1917 are illustrated by the figures in Table XXIII.

TABLE XXIII

	URBAN	RURAL
Michigan	2.0	2.4
New York	1.2	2.8
South Carolina	22.7	47.5
Tennessee	15.9	19.4

In the reduction of dysentery deaths the cities have outdistanced the rural communities. For every 100 deaths in Indiana rural districts in 1900 there were 71 in the cities. In 1917 for every 100 in Indiana rural districts there were 59 in the cities. The same is true in Massachusetts, New Jersey and New York. There is no appreciable change in the urban-rural ratio in either Connecticut or Michigan.

Dysentery deaths are more frequent among the colored than among the white, the only exceptions being in the rural districts of Kentucky and the cities of Virginia.

TABLE XXIV

STATE	ANNUAL RATE PER 100,000—1917			
	URBAN		RURAL	
	WHITE	COLORED	WHITE	COLORED
Kentucky	5.7	11.1	15.6	14.4
Maryland	2.1	4.3	5.7	10.2
North Carolina	12.8	26.6	22.5	32.8
South Carolina	14.6	32.6	42.5	51.8
Tennessee	14.8	18.2	17.9	26.5
Virginia	15.0	12.9	16.5	20.6

With regard to the deaths credited to diarrhea and enteritis we will find the records of the Metropolitan Life Insurance Company, Industrial Department, of special interest. These figures do not include children under one year as this age group is not insured. From 1911 to 1916, 14,173 deaths were charged to this cause. This accounted for 2.2 per cent of the entire mortality and represented a death rate of 26.3 per 100,000. The death rates by age groups are shown in Table XXV.

TABLE XXV

AGE	RATE
1 to 4	208.7
5 to 9	8.8
10 to 14	2.4
15 to 19	1.9
20 to 24	2.8
25 to 34	4.5
35 to 44	7.7
45 to 54	10.9
55 to 64	28.2
65 to 74	80.3
75 and over	182.5

Diarrhea is most prevalent at the extremes of life, under 5 and over 74. The lowest rate is at age group 15 to 19. By referring to the chapter on typhoid it will be seen that the age distribution of these two causes is altogether different, the high rates for typhoid occurring among young adults. The age grouping of dysentery deaths is quite similar to diarrhea, the high rates occurring at the extremes of life.

TABLE XXVI

DEATHS FROM DYSENTERY

U. S. REGISTRATION STATES—1915

AGE	DEATHS	RATE PER 100,000
0- 9	985	7.1
10-19	33	0.27
20-29	48	0.41
30-39	57	0.63
40-49	68	1.03
50-59	119	2.64
60-69	223	8.37
70 and over	634	41.0

During the World War our troops were relatively free from dysentery. From October, 1917, to August, 1918, the admission rates from this cause were usually less than 1 per 1000, both in this country and abroad. The rate remained about the same for the balance of the year among the troops on this side, but in the Expeditionary Force they rose to 3, 4, 5 and even 7.9 for certain periods during the late autumn. Dysentery was about 3 times as prevalent as typhoid among the troops in this country during the summer of 1918 and about twice as prevalent as typhoid in the last four months of 1918.

For the entire year 1918 there were 3573 admissions for dysentery among a mean army strength of over two and a half million men. About three-fourths of these admissions occurred in the expeditionary force. The admissions classified by type of disease and location of troops is shown in Table XXVII.

TABLE XXVII

TYPE OF DYSENTERY	TOTAL ARMY	ARMY IN U. S. AND ALASKA	ARMY IN EUROPE EXCLUDING RUSSIA	ARMY ELSEWHERE PHILIPPINES HAWAII, PANAMA, ETC.
Total	3573	883	2431	259
Bacillary	325	70	244	11
Balantidic	6	2	4	0
Entamoebic	428	239	105	84
Other Protozoa	30	14	15	1
Unclassified	2784	558	2063	163
Mean Strength	2,518,499	1,381,429	1,046,534	90,536

The largest group of dysentery cases was unclassified. The entamoebic type was next in frequency and, considering the number of men exposed, this was most prevalent in the Philippines. Bacillary dysentery was most common in the European forces.

Among the 3573 cases during the entire year 1918 there were 53 deaths, 8 from bacillary dysentery, 11 entamoebic, 3 other protozoa, 31 unclassified. The case fatality in the entire group was 1.5 per cent, bacillary 2.5 per cent, entamoebic 2.6 per cent, other protozoa 10 per cent, unclassified 1.1 per cent.

Bibliography

- ANNESLEY, JAMES: *Researches into the Causes, Nature, and Treatment of the More Prevalent Diseases of India, and of the Warmer Climates Generally*, Sec. Ed., London, Longman, Brown, and Green, 1841.
- ARETAEUS: *Causes and Signs of Acute and Chronic Disease*: translated by Reynolds.
- BAHR, P., AND WILLMORE, J. G.: *Quar. Jour. Med.*, 1918, xi, 349.
- BARTLETT, G. B.: *Quar. Jour. Med.*, 1917, x, 185.
- BASS, C. C., AND JOHNS, F. M.: *New Orleans Med. and Surg. Jour.*, 1914, lxxvii, 456.
- BONTIUS, J.: *An Account of the Diseases, Natural History, and Medicines of the East Indies*, London, 1769.
- CASTELLANI, A., AND CHALMERS, A. J.: *Manual of Tropical Medicine*, Third Ed., New York, William Wood & Company, 1919.
- CLEGHORN, G.: *Observations on the Epidemic Diseases in Minorea in the Years 1744-1749*, Fourth Ed., London, 1779.
- COUNCILMAN, W. T., AND LAFLEUR, H. A.: *Johns Hopkins Hospital Reports*, 1891, ii, 395.
- CRAIG, C. F.: *The Parasitic Amoebae of Man*, Philadelphia, Lippincott Company, 1911; *Military Surgeon*, 1917, March and April.
- DOBELL, C.: *The Amoebae Living in Man*, New York, William Wood & Company, 1919.
- FANTHAM, H., AND PORTER, A.: *British Med. Jour.*, 1916, ii, 139.
- HARRIS, H. F.: *Med. News*, 1894, lxxv, 567; *Am. Jour. Med. Sc.*, 1898, cxv, 384; *Arch. f. Path. Anat.*, 1901, clxvi, 67.
- HAUGHWOUT, F. G.: *Phil. Jour. Sc.*, B. *Trop. Med.*, 1918, xiii, 217.
- HIPPOCRATES: *Genuine Works*; translated by Adams, published by the Sydenham Society.
- HIRSCH, A.: *Handbook of Geographical and Historical Pathology*, London, New Sydenham Society, 1886.
- HUBER: *Deutsch. Med. Wehnschr.*, 1903, xxix, 267; *Berlin klin. Wehnschr.*, 1906, xliii, 1609; *Zeitschr. f. klin. Med.*, 1909, lxxvii, 262.
- KARTULIS, S.: *Arch. Path. Anat.*, 1885, xcix, 145; *Centralbl. f. Bakt.*, 1887, ii, 745; *ibid.*, 1904, xxxvii, 527; *Kolle u. Wassermann's Handb. d. Pathogen. Mikroorg.*, 1906.

- KENNEDY, A. K., AND ROSEWARNE, D. D.: *Lancet*, 1916, i, 1163.
- KOFOID, C. A., KORNHAUSER, S. I., AND SWEZY, O.: *Arch. Int. Med.*, 1919, xxiv, 35.
- KOVÁCS, F.: *Zeitschr. f. Heilkde*, 1892, xiii, 509.
- KRUSE, W., AND PASQUALE, A.: *Zeitschr. f. Hygiene*, 1894, xvi, 1.
- LÖSCH, F.: *Arch. f. Path. Anat.*, 1875, lxv, 196.
- LYNCH, K. M.: *New York Med. Jour.*, 1915, ci, 886.
- PRINGLE, J.: *Observations on the Diseases of the Army*, Sixth Ed., London, 1768.
- QUINCKE, H., AND ROOS, E.: *Berlin klin. Wehnschr.*, 1893, xxx, 1089.
- RHAMY, B. W., AND METTS, F. A.: *Jour. Am. Med. Assn.*, 1916, lxvi, 1190.
- ROOS, E.: *Arch. f. Exp. Path. u. Phar.*, 1894, xxxiii, 389.
- SCHAUDINN, F.: *Arb. kaiserl. Gesundh.—Amte* 1903, xix, 547.
- SMITH, A. J., AND BARRETT, N. T.: *Jour. Parasit.*, 1915, i, 159.
- SMITHIES, F.: *Am. Jour. Med. Sc.*, 1912, cxliv, 82.
- STILES, C. W.: *Washington Med. Annals*, 1902, i, 64.
- SWEET, W. C.: *Jour. Am. Med. Assn.*, 1921, lxxvi, 1819.
- VAUGHAN, V. C.: *Infection and Immunity*, *Am. Med. Assn.*, 1915.
- WALKER, E. L.: *Phil. Jour. Sc.*, 1911, vi, 259.
- WALKER, E. L., AND SELLARDS, A. W.: 1913, viii, 253.
- WENYON, C. M.: *Lancet*, 1915, ii, 1173.
- WOODWARD, J. J.: *The Medical and Surgical History of the War of the Rebellion*, vol. i, part 2.
- YOSHIDA, K.: *Jour. Exper. Med.*, 1920, xxxii, 357.

CHAPTER XIV

SPRUE

Stomatitis Intertropica; Diarrhea Alba; Psilosis

Description.—Sprue is a chronic, insidious, slowly progressive, grave disease of the submucosa of the alimentary tract. It usually begins with sore mouth, indigestion, and morning diarrhea, with abundant frothy discharges. The symptoms are at first intermittent, evanescent, and awaken but little concern on the part of the infected person. It is quite evident that the primary lesions are in the submucosa, indicating infection through the blood supply. In the submucosa there is congestion, with thrombosis of the vessels and consequent exudation accompanied by round-celled infiltration. As a consequence of these alterations in the deeper tissue, the mucosa undergoes necrotic changes with the formation of numerous small ulcers. These changes may begin in any part of the alimentary canal, though in most instances they are at first most marked in the mucous membrane of the mouth. In advanced cases the greater part of the alimentary canal may be more or less involved. The dorsum of the tongue, the inside of the cheeks, the esophagus and the stomach, as well as both small and large intestines, suffer from the congestion and ulceration. This condition interrupts normal digestion and, in fact, renders the taking of any kind of food painful and its proper digestion and absorption impossible. The tongue shows a whitish fur with projecting fungoid papillae. Its tip and edges are highly inflamed and present multiple patches studded with small vesicles and ulcers. The oral cavity is sometimes filled with a tenacious mucus which clings to the fauces and posterior wall of the pharynx. Attempts to remove this secretion lead to nausea and in some instances to vomiting; in short, there is a rawness of the alimentary canal which, although varying in degree in different parts, may affect this tube from end to end. Naturally, it is impossible for one in this condition to maintain his weight. Slowly the body is emaciated, the skin hangs loosely in folds, and there may be marked edema, especially about the ankles. Usually there is great discomfort in the stomach and intestines in the early morning, which is partially relieved for the rest of the day by one or more copious discharges of highly offensive, frothy feces. The condition of the patient necessitates the discontinuance of every activity, rest in bed, and confinement to some simple diet, milk or milk and fruit being generally employed. The causative

agent has not been determined; although at present the weight of evidence indicates that a yeast, *Monilia psilosis*, is a factor, possibly primary, more probably secondary, in the production of the lesions.

Manson, whose studies have contributed much to our knowledge of this disease, writes as follows:

“By the term ‘sprue’ is understood a peculiar and very dangerous form of chronic catarrhal inflammation of the whole or part of the mucous membrane of the alimentary canal, generally associated with disturbance of the chologenic function of the liver, and probably, of the functions of other glandular organs subserving digestion. Although a disease of warm climates it may develop for the first time in temperate climates; only, however, in individuals who have previously resided in the tropics or subtropics.

“Sprue is characterized by irregular alternating periods of exacerbation and of comparative quiescence; by an inflamed, bare, and eroded condition of the mucous membrane of the tongue and mouth; by flatulent dyspepsia; by pale phenomenally copious and generally loose, frothy, fermenting stools. By wasting and anemia; and by a tendency to relapse. It may occur as a primary disease, or it may supervene on other affections of the bowels. It is very slow in its progress; and, unless properly treated, tends to terminate in atrophy of the intestinal mucosa, which usually, sooner or later, proves fatal.”

This disease is most prevalent among whites who are living in tropical or subtropical countries, although natives are not wholly free from it. It is generally believed that when the first evidence of the disease appears in one who has come to the tropics, return to his home is quite essential to recovery.

At autopsy the essential lesions are confined to the alimentary canal, and in some instances the mucosa of the small intestine is found to be almost entirely destroyed. Atrophy of the liver is quite common and a like condition may be found in the spleen and pancreas. Histologically, however, these organs are not uniformly involved.

History.—The first description of the disease now known as sprue appears in a unique volume, entitled, “Observations on the Changes of the Air and Their Concomitant Epidemical Diseases in the Island of Barbados,” by William Hillary. The first edition of this book was published in 1752. We have before us the second edition bearing the date of 1766, from which we make the following quotation:

“Having treated on such *acute diseases* in the preceding part, as are either peculiar to or endemical in the West India Islands, and such countries as are situated within the torrid zone, and are not so frequently seen in most parts of Europe; I shall here speak of such *chronical diseases* as are either indigenous or endemical, in the same warm countries, and are unknown and never seen but in the hot climates, except when they are carried by the sick into the colder countries.

“And I shall begin with the description of a disease, which I think I may safely say is new and has never yet been described by any author, neither ancient nor modern, not even by any of the *Arabian physicians*; most of whom lived and practiced in the

hot countries of *Persia*, *Syria*, *Arabia*, and *Egypt*; but of late years is become endemical and frequent in Barbados, and the other West India Islands.

“From the best accounts that I can obtain, this malady has been some chance time seen in this Island, near these 30 years, though but very seldom; and after I came there in 1747, I did but see one person who had it, in the first four years of my residing there; and three more in the next three years; but within the four last years past, it has become so frequent, that I have seen some scores of patients laboring under it, yet it seems not to be in the least infectious or contagious.

“The patient who labors under this disease usually first complains of an uneasy sensation, or slight burning heat about the cardia, or upper mouth of the stomach; which comes slowly on, and gradually increases, and rises up the esophagus into the mouth, without any fever, or the least feverish heat, or much pain attending it; most commonly without any observable intemperance or irregularity in living, or without any surfeit, taking cold, or any sort of fever or other disorder, which it can be attributed to, preceding it, or any manifest or immediate cause, to which it can be ascribed.

“Soon after this burning heat, little small pustulae, or pimples filled with a clear acrid lymph, no bigger than a pin’s head begin to rise; generally first on the end and sides of the tongue, which gradually increase in number, not in magnitude, and slowly spread under the tongue, and sometimes to the palate and roof of the mouth, and the inside of the lips; and soon after the thin skin which covers those pustulae, slips off, and the tongue looks red, and a little inflamed, though not swelled, yet is almost raw like a piece of raw flesh, and is so tender and sore, that the patient can eat no food but what is soft and smooth, nor drink anything that is vinous, spirituous, or the least pungent, without acute pain; so that some suffer much from the want of proper food. In some, pytalisme comes on, and continues a long time, which is so far from being of any service, or giving any relief to the patient, that on the contrary it drains and exhausts the fluids of the body and greatly wastes and sinks them.

“In this state they continue several days, or weeks, and sometimes for months, sometimes a little better, then worse again; and after a considerable time, sometimes longer, and sometimes shorter, the pustulae will disappear and the mouth grow well, without any medicines or applications, or any manifest cause, and continue so for several days or weeks; but soon after this, the patient finds a burning heat in the esophagus and stomach, attended with ructuses and sometimes vomitings, by which a clear acrid lymph, or waterish phlegm, which is very hot, and most commonly very acid, is brought up; though in some few it is not so acid; this generally continues but a little time before a diarrhea comes on, and continues a longer or shorter time in different patients, and sometimes for a longer or shorter time in the same person, and in some it continues for many weeks; and in all it greatly wastes their flesh and strength, and sinks their spirits very much. The diarrhea after continuing a longer or shorter time, sometimes stops without taking any medicines, or doing anything to stay it, and the patient thinks himself better for a short time, and sometimes for a longer time; but in general the acrid humor soon returns to the mouth again, with all the same symptoms, but somewhat increased or aggravated; and after some stay there it removes from thence to the stomach and bowels again; and thus a metastasis of the humor from the mouth to the bowels and *vice versa*, is frequently, and sometimes suddenly made, without any manifest or perceptible cause. Some chance time, though but seldom after the disease has continued a long time, it affects all the *primae viae* from the lips to the anus at the same time, and excoriates the last; and I have observed in one or two cases where the pustulae appeared about the genital parts

as we sometimes find the aphthae do, as *Hippocrates* observes; and in one or two cases I observed it to break out like an impetigo, about the mouth.

“The patients are all along without any fever or feverish heat, and their pulse is all this time rather smaller, lower, slower, and more languid than it was when they were in full health; and their body and countenance rather paler and somewhat colder, especially in the extreme parts, than when they were well; no thirst, except what the diarrhea causes, when it continues long, and that generally moderate. The patient’s skin is generally dry, all the time of the disease, and he perspires very little.

“The frequent metastases which this acrid humor makes from the mouth to the stomach and bowels, and from those to the mouth again, greatly emaciate, weaken and consume the patient. For when it is in the mouth, both it and the tongue are so excoriated, raw, tender and sore, that they can take no nourishment, but such as is very soft, smooth and mild, and in a liquid form, without giving them exquisite pain: and when it is in the stomach, it gives a painful burning sensation, and a frequent gulping up, or vomiting a little clear, acrid, acid liquor and their food also; so that the stomach can retain and digest nothing but what is very soft, smooth and light, and sometimes not even that. And when the humor falls upon the intestines, it produces a diarrhea with a sense of heat, and sometimes a griping (tho the last not often) and sometimes with hot stools and a tenesmus; so that most of the nutritious juices run off that way which greatly wastes and sinks the patient. These circumstances continuing, and the disease frequently changing from place to place almost continually deprives the sick of their proper nourishment, whence a true *atrophy* is produced, which at the last, either sinks the patient, or brings on a *marasmus*, which soon ends in death.

“This is a true and I think an exact description of this disease, and its symptoms, which too often seizes several of the inhabitants of Barbados, and I believe of the other West India Islands also, and has been too often fatal to several of them.

“The nature, symptoms, and appearance of this disease, are considerably different from those of the true *aphthae*, either of the ancients or moderns. The true *aphthae* generally are, either attended with a fever, or immediately follow a putrid fever, an irregular intermitting fever, a dysentery, a diarrhea febrilis, or some other fever: this comes on gradually, slowly, and almost imperceptibly, and always without any fever, either preceding or accompanying it. The *aphthae* are much larger pustules, and either suppurate and fill with a concocted matter and form little ulcusculeae, or turn black and gangrenesce: these are much smaller, and fill with a clear acrid lymph, or ichor, and then excoriate the parts; but rarely or never fill with matter, except here and there a chance pustula when the disease has continued long; but never form ulcusculeae, nor gangrenesce. These usually seize people advanced in years, rarely youths, and never children: the *aphthae* most frequently seize children, rarely youths, and sometimes people in years, but most commonly either with, or immediately after they had a fever; this is never with a fever, but on the contrary, they generally have a small, low, and languid pulse, and are usually colder than in health. The *aphthae* are but of a short duration, and is an acute disease, and usually either kills the patient or they recover in two or three weeks’ time, or less; but this disease continues with short intervals of being a little better, then worse again, for several years, before it puts an end to life; I am informed that it has continued for eight or nine years in some patients before it was fatal; though it has been so to some others in less than a year, when they had lived too freely, or did not seek for proper assistance.

“It also differs considerably, and in many respects, from an *erysipelas*, or an *erysipelatoïdes*; and also a little in some respects from an *impetigo*, though it is in

some respects most like that, and if it was external would probably produce scaly scabs on the skin after the pustulae broke, as I once saw it about the mouth.

“As it is a new disease, we must give it some name; shall we call it an *Aphthoides chronica*, or an *Impetigo primarum viarum*? or what? But I will not dispute with any about its name, as that is only a dispute about words; and if any person will give it a better name, I will readily agree with him, and thank him also.”

Hillary goes on to speculate about the cause of this disease and concludes that it is due to the suppression of excretions through the skin and the turning of these poisonous substances into the intestinal tract. He concludes that this might result from sudden chilling of the surface from cold bathing, wet clothing, lying on damp sheets, or from some other circumstance which might interrupt the normal flow of the perspiration. Having arrived at a satisfactory explanation of the cause, Hillary directed his treatment to cleansing out the alimentary canal and restoring the normal action of the skin. For the first purpose he resorted to cathartics; for the second he employed ipecac, and he placed great stress upon the value of hot baths. There being no natural hot mineral baths on the Island, he recommended that his European patients return to their homes and enjoy the waters at Bath, Aix-la-Chapelle, and like places. For those who could not well return to Europe and for the natives, he attempted to provide artificial mineral waters, but found these unsatisfactory. He states that some of his patients who did return to Europe and take the mineral baths made complete recoveries and came back to the Island in perfect health, while among those who did not go to Europe and take the baths the results were less satisfactory. It is more than probable that the European baths did not give all the benefits that came to those who left the Island.

It appears that the word sprue, or the Dutch word sprouw, is used in Holland and the Scottish Lowlands to designate a frequent disease in children, characterized by aphthous patches. As early as 1687, Ten Rhyne, a Dutch physician in the East Indies, described certain lesions of the mouth, intestines, and esophagus, under the name Indische spruv or sprouw. English physicians in the Orient have adopted the Dutch word and anglicized it in the present form. Thin has proposed the more scientific term psilosis, from the Greek word meaning bare or raw. This term, however, is hardly suitable, unless it be definitely modified, as *Psilosis linguae, vel mucosae intestini*; indeed, this is the full name as recommended by Thin.

English physicians, Twining (1835), Grant (1854), and Cunningham (1877), described a disease, from the symptoms of which it is clearly indicated that these men were dealing with sprue, but in no instance do we find in these writings an improvement on the descriptions given by Hillary. Twining wrote of a white flux following dysentery and charac-

terized by abundant, watery, frothy stools. Grant was one of the first to describe the hill diarrhea of the Himalayan Stations and he pointed out that it is not confined to those exhausted by previous disease but often attacks persons in the prime of life and with a good health record.

A few years later, Moore, in his work, entitled, "A Manual of the Diseases of India," claimed that the hill diarrhea does not differ from the Diarrhea alba of the Indian plains, and wrote the following description of this disease:

"The symptoms of Diarrhea alba are usually painless, but sometimes painful, purging occurring at first principally in the morning. The stools may at first be bilious looking, but are often from the commencement, and always afterwards, light, almost white in color. They are also copious and frothy. As the disease advances, light stools are also passed in the evening, but the patient, probably continuing to feel tolerably well, takes little notice of the commencement of the malady. The calls to stool, although generally unattended with pain, are urgent, but the feces are passed without straining or faintness, and are succeeded by a feeling of comfort. The most annoying symptoms are fullness and distention of the bowels by flatus, and eructations having the flavor of rotten egg. At first the stools themselves are not offensive, although afterwards becoming very much so. Often no very abnormal sensation is felt in the region of the liver, but sometimes from the very commencement there is an uneasy sensation. When this is inquired into, it is found to be rather a feeling of void than fullness, as if the ribs were about approximating. As the disease advances, the appetite at first good, becomes the reverse, the pulse grows more feeble, the tongue is furred in the center, and faintness may follow the stools. There is sometimes, at a later period, some degree of sallowness, and a bronzing, similar to that in Addison's disease, has been noticed. If the malady is not checked, the person falls into a state of confirmed cachexia. The stools become more numerous, progressive emaciation takes place, the mind becomes weak and fretful, and fever may occur. Then, probably, the stools become dysenteric, and the patient dies exhausted."

Thin is inclined to question the identity or even the close relationship of the white diarrhea of India with sprue. He calls attention to the fact that in the discussion of the white diarrheas by English physicians there is not enough stress placed upon the condition of the tongue to justify the identification of these diseases with sprue. Furthermore, he is quite certain that sprue does not follow dysentery, but is in practically all instances a primary disease. On the other hand, Manson states that sprue may follow dysentery or acute enterocolitis and that there are cases of sprue in which the lesions and symptoms are confined to certain parts of the alimentary canal, while the condition of the mouth is not bad enough to attract special attention. On this point he writes:

"When the disease has supervened on dysentery, we learn that the motions characteristic of the original dysenteric attack had gradually changed in character; from being scanty, mucoid, bloody, and accompanied with pain and tenesmus, they became diarrhetic, pale, frothy, their discharge being followed by a feeling of relief rather than of pain. The mouth at the same time became sore, exhibiting the characters

already described. Gradually a condition of confirmed sprue was established, which ultimately, unless properly treated, will almost certainly prove fatal.

"Another type of case commences as an acute enterocolitis with sudden and profuse colicky diarrhea, vomiting perhaps, and a certain amount of fever. The acute symptoms do not subside completely, but gradually have the typical symptoms of sprue grafted onto those of an acute intestinal catarrh.

"Occasionally we meet with cases of confirmed sprue in which, at first, the morbid process, judging from the existing clinical symptoms and subsequent history, is confined to a limited part of the alimentary canal. Thus we sometimes get sprue without diarrhea, the principal symptoms being sore mouth, dyspeptic distention, pale, copious but solid stools and wasting.

"On the other hand, we may get cases in which the mouth is not eroded, and in which there is little or no distention or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient who may have suffered at an earlier period, or on a former occasion from the first type of the disease, later acquires the diarrhetic form; and *vice versa*.

"It sometimes happens that under treatment the sore mouth, the dyspepsia, and the diarrhea completely subside; nevertheless the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition."

In 1880 Van der Burg, a Dutch physician in Java, published a prize essay on "Indische Spruw," in which he divides the course of this disease arbitrarily into three stages. In this book the symptomatology of sprue is given quite exhaustively, but there is nothing satisfactory regarding the etiology except that the author reaches the important conclusion that neither alcohol nor malaria is concerned in the causation. He states that it is much less frequent in the natives than among Europeans; that the disease does not attack new arrivals; that most of those affected have reached middle age, but it may occur at both extremes of life; that females are more frequently affected than males, and that pregnancy predisposes to the disease.

Since the time of Hillary sprue has apparently disappeared from, or at least has become very rare in, the West Indies, even in Barbados where Hillary studied it. As we have already stated, the Dutch physicians in Java gave this disease its name and made most valuable contributions to its symptomatology and history. In Ceylon, what is now known to be sprue, has prevailed through many years under the designation of "Ceylon sore mouth." Sprue is quite widely distributed through China, both north and south, and the earliest cases of this disease seen by American physicians were whites who had been residents of China for many years. Some of the earliest cases have been missionaries to that country. In the latter half of the nineteenth century the fact that sprue is frequent in Java and through the East Indian Islands, in north Borneo, and in the Malay Peninsula, was recognized

by physicians visiting and temporarily located in these countries. With the first occupation of Cochin China (1861) by the French an epidemic diarrhea began to harass both the soldiers and those civilians who followed the military occupation. Out of a total of 9,223 French soldiers and sailors in Annam during the year 1864, there were 3,501 cases of intestinal disease with 198 fatal results. Of the deaths, 85 were due to Asiatic cholera and 113 to the prevalent diarrhea. For years there were active discussion and difference of opinion among French physicians who studied the diarrhea of Cochin China. This discussion was opened by Jullien who, in 1864, made a valuable report founded upon 108 autopsies. Jullien appears to have been somewhat in doubt whether the diarrhea which he studied should be regarded as a modified dysentery or as a disease *sui generis*, although he was inclined to the latter opinion. In his autopsies he was struck with the infrequency of hepatic abscess and he, for this reason, questioned the propriety of assuming or concluding that the disease was a form of dysentery. Other French physicians were inclined to regard the Cochin China diarrhea as a modified dysentery, and finally it came to be known as "dysenteric diarrhea." While valuable papers came from French physicians, they dealt principally with the question of the dysenteric or nondysenteric character of the disease. It will be understood that this controversy arose some years before Manson, in China, and Van der Burg, in Java, established beyond doubt the specific nature of sprue and gave it this name. There is at this time a general agreement that Cochin China diarrhea about which French physicians wrote so much and to the knowledge of which they contributed so largely, is sprue.

There has been a like discussion concerning the diarrheas of India and adjacent countries by English physicians. As early as 1854 Grant, in a paper which has since become classical, described a diarrhea prevalent at the Indian Hill Stations at elevations of from 4,000 to 8,000 feet. According to Grant, the state of the tongue and mouth in this hill diarrhea is quite characteristic. The tongue carries superficial ulcers and deep indentations along the margin, while the gums are congested and bleed easily. In some the tongue is white with streaks of red. About the edges it becomes raw, fissured, dry and rough, and there is difficulty in swallowing. Usually this diarrhea comes on without nausea and griping, but call to stool is frequent and urgent. The stools are described as drab or muddy gray in color, frothy, and feculent. As the disease progresses they become white, pultaceous and yeasty. Stools are most frequent between daylight and breakfast and again as evening approaches. Grant states that the odor of the stool is peculiarly unnatural, but not offensive. The odor is, however, modified by the

food. This disease, or at least the worst forms of it, is accompanied by progressive emaciation. Evidently, assimilation and nutrition are perverted and finally quite destroyed. This progressive emaciation is in many instances accompanied by edema of the legs and dropsy of the abdomen. Mental weakness accompanies this physical deterioration and the patient becomes fretful, vacillating, and incapable of consecutive and rational thinking. The cause of hill diarrhea remains unknown and its relation to sprue is still a matter of discussion among English physicians in India.

In 1908 Brown published a valuable monograph on sprue, and in this he discusses the relation between hill diarrhea and sprue. It seems that hill diarrhea, in many instances at least, comes on as an acute, infectious disease, characterized by a chill followed by a fever. It may appear among the robust almost immediately after reaching one of the hill stations. Grant thought it confined to four stations: Simla, at an elevation of from 6,500 to 8,000 feet; Dagshai, 24 miles from Simla and 6,000 feet high; Subathoo, 22 miles from Simla and 4,000 feet, and Karauli, 32 miles from Simla and 6,400 feet high. Brown is quite certain that hill diarrhea is not identical with sprue. It seems that this conclusion is justified by the suddenness with which hill diarrhea makes its appearance, by the fever which accompanies it, and by the morbid anatomy which apparently differentiates the two diseases. All pathologists who have studied sprue agree that the primary invasion of the alimentary canal is through the submucosa. The suddenness of onset in hill diarrhea and the histologic findings after death certainly justify the conclusion that this disease is not identical with sprue.

Brown gives the following general description of hill diarrhea:

"Hill diarrhea is a disorder of the digestive system, which although not confined to high altitudes, usually affects residents of the more elevated districts of the eastern tropics, and is especially prevalent in some of the sanatoria and hill stations of India. In typical instances, it assumes the form of an alcoholic gastrointestinal catarrh, the symptoms being nausea, abdominal pain and diarrhea. The evacuations are most frequent in the early morning, and are loose, copious, frothy and colorless. In its nature, hill diarrhea is less malignant than sprue, and as a rule it is readily amenable to treatment; but occasionally it is complicated by choleric seizures, and, not infrequently, it passes into a chronic and somewhat intractable condition. Though all classes and races are subject to this disorder, Europeans are principally affected, visitors who have recently arrived from hot, low-lying districts being particularly liable to attack."

Hill diarrhea is not the only disease in India whose relation to sprue has been a matter of doubt and discussion. In the Lettsomian Lectures for 1881, Fayrer discusses, under the title of, "Chronic White Tropical Diarrhea," a disease which is said to be highly prevalent among Europeans in India and quite unresponsive to treatment. Fayrer believed

this disease to be one capable of differentiation from hill diarrhea and, indeed, from all other diarrheas characterized by colorless stools. The description of chronic white tropical diarrhea conforms satisfactorily to that of sprue. It seems to be the consensus of opinion of competent men who have worked in the Orient that the Cochin China diarrhea described by French physicians and the chronic white tropical diarrhea discussed by Fayrer and others are sprue.

As we have already stated, in 1908 Brown wrote a monograph on sprue in which he assembled practically everything of value known up to that time. As to the relation between sprue and dysentery, Brown wrote as follows:

"Sprue and dysentery are distinct diseases, and owe their origin to different causes; but both are of every-day occurrence in certain parts of the eastern tropics, and it is not surprising that they should frequently be seen in combination. In such instances the usual sequence of events is that the illness commences with acute dysentery, which, without evidence of amoebiasis, gradually becomes chronic; that, after some weeks, the dejecta cease to be dysenteric, their appearance now being suggestive of sprue; that about the same time the tongue and mouth are found to be affected by characteristic lesions, and that there are also symptoms of toxemia. The after-history is usually such as is seen in the ordinary course of sprue. But it is also the case that, in certain localities and in particular outbreaks, sprue assumes a distinctly inflammatory type. The usual progressive and uneventful course of the disorder is then interrupted by intercurrent seizures of dysenteric diarrhea. In the low country of the Dutch Indies and Malaya this form of sprue is rare, but in the hill districts of Ceylon and Java, and notably in Cochin China, where they are known as '*crises dysenteriques*,' these attacks are common and severe. At periodic intervals during what appears to be the ordinary progress of sprue, the patient is seized with sharp abdominal pain followed by tenesmus and the passage of mucus and blood. According to severity, the attacks are of longer or shorter duration, and they may or may not be accompanied by fever; but in Cochin China they usually last about two or three days; the rise of temperature is slight; and as a rule they are easily amenable to treatment. It is, of course, possible that such seizures may be produced in an otherwise uncomplicated case of sprue by exceptional ulceration in the sigmoid flexure or rectum; but in view of our present knowledge of the causes of dysentery, there can be no doubt that most of them are genuine instances of a double infection. Probably, however, chills and unsuitable food are the important factors in causation, for it is certain that in Cochin China at least occasional dysenteric diarrhea does not betoken the combination of the two diseases. When sprue and dysentery occur together the former, except in fatal cases, being the slower process, outlives the latter, and is often seen as the terminal stage. It appears to persist after the exhaustion and death of the pathogenic agent of dysentery, whether bacillary or amoebic, and is probably responsible for its disappearance."

Brown's chapters on symptoms, morbid anatomy, and prevention of sprue are valuable. In discussing the morbid anatomy he brings out a point which should always be held clearly in mind by the epidemiologist; and that is that in sprue the primary intestinal lesions originate in the submucosa. This indicates that the path of invasion taken by the

virus, whatever it may be, lies through the blood or lymph supply. This virus, it is true, may be formed in the lumen of the intestine, but it operates only after absorption into the blood or lymph and its predilection tissue is in the submucosa. The effects on the mucosa, which, as the disease establishes itself become more and more prominent and at autopsy dominate the pathologic picture, are secondary. We regard as so important the distinction between sprue and dysenteries and diarrheas that we add hereto a short quotation from Brown's chapter on morbid anatomy:

"Under the microscope it is seen that, as in other parts of the alimentary canal, the lesions of the small intestine originate in the submucosa. The vascular network of that tissue is congested and distended by thrombi; and when these are of long standing, the pigment of the blood soaks through the vessel walls, and, becoming absorbed by the superficial cells, stains them the peculiar leaden tint that has already been noted. The areolar tissue and lymphatic channels are packed by a condensed infiltration of small round cells, which compresses and obliterates the crypts of Lieberkühn. Not infrequently the lower parts of the crypts escape the strangulation, which involves their outlets and cuts off their communication with the intestinal canal, persist and are seen on section as cystic dilatations in the submucosa. The villi, too, are invaded by embryonic cell growth; the central lymph vessels and the areolar framework become misshapen and distorted by the infiltration; ultimately this is organized and shrinks, and the villi retract and are lost in the general distention of the mucous membrane. The primary effect of these changes is arrest of the blood supply to the mucosa. The surface epithelial cells then lose their nuclei, disintegrate, and are shed into the lumen of the intestine, while necrotic areas, forming where pressure is greatest in the epithelial layer and submucosa, originate the superficial ulceration which is so marked and characteristic a feature of the secondary state of sprue."

After learning the above facts concerning the morbid anatomy of this disease, we can readily understand why sprue is an insidious, slowly developing, disease, and one which is subject to marked recessions and exacerbations; one that interferes with digestion and nutrition and leads to emaciation; one which starves not only the body as a whole, but especially certain organs, such as the liver, and leads to atrophy; one that in its uncomplicated form is free from febrile symptoms; and, finally, one whose treatment is dietetic and not by drugs.

Brown is quite convinced that sprue is a specific infectious disease due to a protozoan, a bacterium, or some other minute poison manufacturer. He states that no other theory will satisfactorily account for the lesions that are found characterizing this disease. He finds further support of the microbial origin of this disease in its regional distribution. There are places, like the Island of Barbados, where sprue was once highly prevalent but is no longer known or is exceedingly rare. There are places geographically contiguous, practically identical in geological formation, in climate, and in the character of its people, their food, dress, and habits; while in one of these localities sprue will be

found in abundance, in the other it is unknown. There is sprue in Shanghai and its environs, while it does not occur in Japanese ports, nor, indeed, in any part of Japan. It is common in Malaya, but is unknown or at least unrecognized, in Central America. There are cases of sprue which apparently have been acquired during short periods of residence in an infected locality. The frequency with which the initial lesions appear in the mouth is held by some to be evidence of the infectious character of the disease. In our opinion, however, this is not very convincing, since the fact which we have just emphasized, that the path of invasion is through the blood or lymph, would not justify the assumption that the point where the poison is manufactured must necessarily be immediately adjacent to the location of the earliest and most pronounced lesions. Brown holds that sprue is a toxemia, but of the nature of the organism which manufactures the poison and of the poison itself, he claims no definite knowledge, and this seems about the conclusion which we shall have to adopt today.

Is sprue indigenous in the United States? In 1915 Wood collected the literature on this subject. According to this author, sprue was recognized in North Carolina before the classical report of its existence in Barbados was made by Hillary. Wood states that, in the *Natural History of North Carolina*, published in Dublin in 1737, Brickell, a Dublin physician who had been sent by the Crown to make a report on the Cherokee Indians, described as prevalent among these people not only yaws, but also a "white flux," which in all probability, Wood says, was sprue. This testimony, in our opinion, is not convincing. There is no account of the symptoms of the disease and the presence of white stools in a diarrhea can scarcely be accepted as a positive diagnosis for sprue. Wood states that in 1905 Graham, of Savannah, reported four cases of sprue which had originated in Georgia. In 1907 Harris, of Atlanta, reported cases of sprue but later concluded that he had mistaken this disease for pellagra. In 1911 Simon, of New Orleans, reported a case of probable sprue of indigenous origin. It will be understood that many American physicians have, from time to time, reported sprue among individuals who have resided in tropical regions, but at present we are confining our remarks to indigenous sprue. Wood thinks that sprue and pellagra are often confounded. He also calls attention to the well-known fact that white stools may result from diseases of the pancreas. In regard to the possibility of confounding sprue and pellagra, Wood says:

"In reviewing my cases, which began in 1905 and include several hundred, I find that at the time of examination the skin lesions were wanting in large number, and a note is made leaving doubt as to the correctness of the diagnosis. In following up these cases it is interesting to note that a considerable proportion never developed the

necessary symptom for such a diagnosis. A number have died of other diseases and only a comparatively small portion were cases of pellagra. A large part of these cases we now know suffered from tropical sprue, which was supposed not to occur in this country. Emphasis should be placed on the fact that in spite of an experience of several hundred cases of pellagra, extending over a period of ten years, any diagnosis made in the absence of skin lesions at that time was simply guess work."

Wood concludes his paper with the following summary:

"(1) Tropical sprue occurs in the southern states, where it is frequently confused with pellagra. (2) Sprue is a definite disease entity with a definite symptomatology, and when followed should cause no difficulty in diagnosis. (3) There is much evidence tending to justify a further study in order to determine whether the characteristic sprue stool is or is not due to a lesion of the pancreas. The deficiency of pancreatic function in sprue may be due to actual pancreatic change, or a disturbed intestinal function may play a part in the findings. (4) The only certain means of differentiation between pellagra and sprue is a study of the feces. Fatty stools with great fat and nitrogen loss are characteristic of sprue, while in pellagra the fat and nitrogen absorption are about normal even in spite of the diarrhea. (5) Sprue may complicate any of the intestinal diseases and add to the confusion in diagnosis, therefore, for the present at least, the diagnosis of pellagra should not be made in the absence of skin lesions except when the history of a former outbreak is definite."

In 1920 Boyd reported two cases of indigenous sprue seen in the clinic of Graves at Galveston. From his studies of the stools of these patients, Boyd finds support for Ashford's contention that sprue is due to a yeast-like organism, which will be described later. Boyd states:

"Manifestations suggestive of sprue may be observed in persons who have never been outside the United States, and from these persons Ashford's monilia may be recovered. Sprue, by reason of the disability it produces as observed in the tropics, is of distinct public health importance. Its importance in the southern United States is as yet undetermined. Potentially it may equal hookworm disease or pellagra, so that every effort should be made to ascertain its incidence and present its characteristics to southern physicians. Our knowledge of its means of transmission is nil, but from the situation in which the organism can be demonstrated it would appear that measures designed to reduce contact and promote proper excreta disposal might be of value in its control."

Etiology.—The theories as to the causation of sprue may be briefly stated as follows: (1) Sprue is not a specific disease; it is a condition or state of the body which may result from any long continued exhausting diarrhea. The fact that the symptomatology is so definite, that the morbid anatomy is so uniform, and that other long continued diarrheas are not accompanied by like symptoms and like lesions, completely negatives this theory. (2) For a time sprue was believed to be due to some intestinal parasite. In Cochin China, worms of various kinds were frequently found in the stools; notably strongyloides, ankylostoma, trichomonas, and others. Continued study, however, showed that there was no uniformity in the intestinal fauna in this disease. Moreover, these worms, singly and in combination, are found in the intestines of people

who never develop sprue. For these reasons the helminthic theory of sprue has been abandoned. (3) From time to time it has been suggested that sprue is due to some dietetic error and nearly every kind of food and drink has been suspected, but even in the early days of this disease in the Dutch East Indies, in China, and on the Malay Peninsula, medical men were struck with the fact that alcohol was not concerned in its causation. American physicians, studying missionaries who returned from the Orient with sprue, reached the same conclusion. Another fact which shows that alcohol has nothing to do with it is that the incidence of the disease is greater among women than among men. For a while, English physicians in India suspected the highly spiced foods which are so popular in that country; but further observation has led them to abandon this supposition. In some regions the increased incidence in sprue was coincident with the greater use of tinned foods and the American manufacturer of these articles was brought under suspicion. This view has also been abandoned. (4) At certain times and in certain places, it has been suggested that sprue is caused by some protozoan and possibly transmitted from man to man, possibly from animal to man, by some biting insect. No such insect has been found to be common to all regions in which sprue originates and the protozoal theory, although at one time or another held by most eminent authorities in tropical medicine, has been abandoned. (5) Quite naturally, the known bacterial world has been searched for the infecting agent, and Rogers and Castellani were at one time inclined to believe that some unidentified strain of the streptococcus might be the guilty agent. Rogers used streptococcic, and Castellani dysenteric, vaccines, but both men apparently have convinced themselves that they were not in the possession of the primary cause of the disease. Rogers thinks that any benefits he might have obtained from his streptococcal vaccine were due to the fact that streptococcic infection, as in many other diseases, is a secondary phenomenon in the development of sprue. The result is that, at present, attention has been diverted from bacterial life. (6) The first suggestion that sprue might be due to a fungus, is usually attributed to Dantec. Soon thereafter (1914) Bahr hit upon the fungus, *Monilium albicans*, which is credited with the responsibility for thrush among children. Ashford has incriminated a closely allied species and the work of this investigator is the most promising line that we have on the etiology of sprue.

In 1909 Ashford, working in Porto Rico, discovered the presence of sprue among the inhabitants of that Island. In 1915 he examined 10,140 persons on the coffee plantations in the mountains about Utuado. Among these he found only 11 cases of complete sprue and 19 doubtful cases.

Most of these were from the town of Utuado, and Ashford states that, in Porto Rico at least, sprue is a disease of towns and cities rather than of rural districts, and that it takes its victims from the higher walks of life rather than from the less sanitary and apparently more exposed poor. He places the average number of cases seen annually by physicians in San Juan at about 25. For some seven or eight years now, Ashford has been trying to solve the problem of the etiology of this disease as seen in Porto Rico. He has fixed upon a species of yeast belonging to the genus *Monilia*, and the species which he has incriminated he has named *M. psilosis*. This is related to, but is not identical with, the better known species of this genus, *M. albicans*. *M. psilosis* is a large, spherical yeast, with a diameter usually varying from four to seven microns. The cell contains a few granules, a vacuole, and a nucleus. In gelatin stab cultures it elaborates mycelium filaments, with the well-known picture of an inverted pine tree. The hypha is clear, contains but few granules, varies in thickness from two to five microns and in length may measure 1,000 microns. It may exhibit branching forms, but these are not common. It does not liquefy gelatin and does not acidify or coagulate litmus milk. It supplies most characteristic and satisfactory growths on Sabouraud's glucose agar, on which it appears as a soft, creamy, elevated growth, with well-defined margins, and generally with mycelium projections into the substrate. It uniformly ferments glucose, levulose, and maltose; frequently, saccharose; and occasionally, galactose. Ashford finds that primary cultures of this organism are not sufficiently virulent to kill laboratory animals, but that the virulence may be enhanced sufficiently to make the organism quite pathogenic to rabbits, guinea pigs, and rats. Among laboratory animals feeding experiments have been somewhat disappointing. A monkey fed on this yeast became weak, morose and emaciated, after developing a sharp diarrhea. *M. psilosis* was found in the stools.

In 1917 Ashford reported that from 68 cases of sprue he had been able to isolate *M. psilosis* in 61, while in 32 control patients, this organism could not be found. Of the total 100 studied, 71 gave positive complement-fixation tests with *M. psilosis* employed as an antigen. This group included all his 68 sprue patients and three of the controls.

Ashford concludes his 1915 paper with the following statements:

"(1) Sprue is usually a mild disease with a veiled picture in which intestinal fermentation is usually present, a tendency to spontaneous cure and a ready submissiveness to a noncarbohydrate diet. (2) Tongue lesions are often clinically and histopathologically indistinguishable from ordinary thrush, a disease due as a rule to *Monilia albicans*. (3) Clinically and histopathologically the picture of the tongue is projected on through stomach to intestine. (4) Chronic intoxication supervenes after well-developed sprue, and the liver atrophies without cirrhotic changes, secondary anemia making its appear-

ance. (5) The intestinal lesions produce large, acid, frothy, white stools with excessive gas production, and full of yeasts. The character of these stools does not warrant the belief that serious ulceration changes take place. (6) There is a tendency to chronicity and to periods of latency in which decided betterment or apparent cure may take place. (7) Drugs are of little avail save when used symptomatically for definite clinical crises and no specific has yet been found."

Ashford found *M. psilosis* in Porto Rican bread, which he says has deteriorated markedly since 1903. He fails, so far as we can ascertain, to give reasons for this deterioration in the bread of Porto Rico. He states that in country districts in Porto Rico, bread is not an article of the daily food, while it is in cities, and to this he is inclined to attribute the fact that sprue is a disease of towns and cities rather than of rural districts, at least in Porto Rico. He says that people of northern birth are more prone than the natives to develop this disease and that family outbreaks are noticeable.

In 1918 Michel, working with Ashford in Porto Rico, reported the results which he had obtained in the treatment of sprue with a vaccine prepared from *M. psilosis*. At that time Michel had treated 81 cases and in 62 the treatment was completed. All cases had been diagnosed by Ashford as sprue and *Monilia psilosis* had been isolated from the feces. Coincident with the administration of the vaccine, the diet was regulated to fit each individual case. Cases of sprue without complications among Americans were found to respond most readily to treatment, recovering more promptly than Porto Ricans. Of 62 patients thus treated, 49 had been discharged cured, 12 were improved and one died.

In 1907 Dold, working in the German Medical School at Shanghai, reported that he had succeeded in developing typical sprue in a young monkey by feeding it on monilia; in fact, he fed two monkeys, father and son, the latter aged eighteen months, on yeast. The older one developed a transient sprue-like diarrhea, but in the younger the disease took a chronic course and terminated fatally five months after the experimental infection took place. The autopsy showed extreme general emaciation with small ulcerations at the margin of the tongue on both sides. The esophagus was normal, but the mucosa of the stomach, small and large intestines was atrophic and showed slight erosions. The liver and pancreas were somewhat diminished but otherwise normal. Histologically, these organs showed no abnormality except a general atrophy. All other organs were normal.

The problem upon which Ashford is at work must be regarded at the present time as incomplete, but the evidence which he has accumulated, year by year grows more convincing.

Castellani has been inclined to regard the presence of yeast fungi in the alimentary canal and in the stool in cases of sprue as merely inci-

dental and points to the fact that mycotic infection is common in healthy people while residing in the tropics.

Racial Incidence.—It is generally stated that sprue is essentially a white man's disease. Still "Ceylon sore mouth" is now generally believed to be sprue and is common among the natives of Ceylon. Some authorities report sprue as not infrequent among the natives of Bombay and Bengal, and Van der Burg found many native cases in Sumatra. There are those who believe, and who present facts substantiating their belief, that there is a deep and inherited susceptibility to this disease in the white race. Whites born in the tropics are apparently quite as susceptible to sprue as those born in temperate and more northern regions. Out of 41 cases among Europeans seen by Rogers in Calcutta, 26 were born in India, and this leads Heaton to say:

"Sprue is thus unique among tropical diseases in attacking principally the acclimatized foreigner, and is usually sparing both the native and the newly arrived European."

English observers of sprue in India and in other parts of the Orient agree that sprue seldom attacks children, either those coming to the tropical country or those born therein. To quote again from Heaton:

"Sprue, as has been frequently observed, distinguishes neither between rich and poor, nor between the robust and the weakly, nor, in adults, between the young and the old. The only unaffected members of the European community are the young children."

Most writers on sprue agree that long residence in an endemic area is essential to the development of this disease. This opinion is, however, not universal and Roux reports a case in which, in his opinion, infection resulted from a short stay in a tropical port during the coaling of the ship. This view is so unusual and exceptional that we must decline to give it credence. When Caucasians develop sprue it is found that the most effective prescription for their treatment is to cut out all carbohydrate food or to reduce this to a minimum; still, natives are less susceptible to sprue and their diet, as a rule, contains more carbohydrates than the Caucasian consumes either at home or while residing in the tropics. It may be that there is some important difference in the methods of preparing carbohydrate foods employed by tropical races compared with those from temperate climates.

Geographical Distribution.—From the evidence at present before us, we must conclude that sprue is distributed quite unevenly throughout the tropical and subtropical belts around the globe. Its areas of greatest prevalence are to be found in India, southern China, and the East Indies. It is less prevalent in northern China, Japan, the West Indies, and the southern United States. Indigenous cases apparently are unknown in the British Isles, in central and northern Europe, throughout

Siberia, in the Dominion of Canada, and in the northern United States. Manson, whose opinion about anything pertaining to sprue carries great weight, says:

“Apparently sprue is most prevalent in those tropical countries in which prolonged high temperature is combined with a moist atmosphere.”

Heaton, who is inclined to attribute sprue to prolonged and marked physiologic deterioration, says:

“The climate where sprue is commonest is that most unfavorable to the maintenance of glandular activity, though its first effect is no doubt stimulating. Prodromata indicative of hepatic hyperactivity are often noted in the history of sprue patients. Children, again, would naturally be immune to a disease caused by exhausted vitality. There are occasional anomalies, it is true, both in the distribution and in the incidence of sprue, and it is often difficult to explain them. The chain of cause and effect in individual cases is admittedly obscure; but the broad facts would not seem to be unintelligible, if the essential cause of the disease is sought, not in a specific infection, but in a faulty or inadequate reaction of the individual to his environment.”

Prevention.—The only author, so far as we can find, who has written satisfactorily concerning the hygiene and prevention of sprue, is Brown, upon whom we must largely rely. There is, however, general agreement, as we have already had occasion to say, among those who have studied this disease, that alcohol, spiced foods, tinned meats, and vegetables cannot be incriminated either as primary or secondary factors in the causation of sprue. Brown says that improved sanitation has had no influence upon this disease. We quote:

“For several years after the occupation of Cochin China by the French, Saigon was perhaps, of all European settlements in the East, the most notoriously unhealthy. Since that time the swamps which surrounded the town have been filled up, and efficient systems of drainage, water-supply and conservancy have been established, with the result that the general health has been much improved. In Saigon itself, malarial fevers, cholera and dysentery are now comparatively uncommon, while in Cholon and the adjoining settlements the rate of mortality from these and similar diseases has been very materially reduced; yet, on the endemic diarrhea of the country, sanitary measures have had little or no influence. In Cochin China, sprue now affects a larger percentage of the resident European population than ever before. And Saigon is but an instance of what may with equal truth be said of other important centers of commerce—of Shanghai, Singapore, Penang, Batavia, Soerabaya and Samarang. In these cities, before the introduction of sanitary supervision, when surface wells formed the sole source of drinking water, and when but little attention was paid to the hygienic requirements of very large populations, sprue was infrequent; and it is a remarkable fact that the extension of a disease which chiefly affects Europeans has been coincident with the introduction of scientific sanitation.”

This is so at variance with the history of the other diarrheas and the dysenteries that it demands special consideration. In the first place, we might question whether the above-quoted statement is founded upon sufficiently extended and exact data to justify its unquestioned accept-

ance. Sprue is a chronic disease requiring many years for its development to the point of clinical recognition and it may be that many of the cases first recognized in recent years had their inception under the old regime when sanitation was notoriously lacking. The other diarrheas and the dysenteries have quite invariably decreased in incidence with improved sanitation, by which we mean the introduction of modern drainage, sewage disposal, and the supplying of unpolluted water. If the statement made by Brown, as above quoted, is true and can be shown to hold good in all areas where sprue is endemic, it seems reasonable to conclude that pollution of soil and water has but little or no influence on its causation and dissemination.

Brown gives the following dietetic maxims, which he thinks may assist in the prevention of sprue and other intestinal disorders found among Caucasians who live in tropical countries:

“(1) When fresh meat (including poultry, game, etc.) can be procured in good condition it should form the chief constituent of two meals daily, if sufficient exercise is taken. (2) Fresh meat is preferable to preserved, tinned or salted flesh of any kind. (3) On account of the liability of meat to contamination, and the rapid development of microorganisms, cold meat should be avoided. And all meat should so far as possible be eaten hot and freshly cooked. (4) When it can be obtained, fresh fish is essentially suited to the dietetic requirements of the tropics, and should always form a substantial item in the daily fare. (5) Vegetables are generally somewhat unsatisfactory, but when they are available they should be utilized. Tinned vegetables are less liable to objection than tinned meat. (6) Fruit should be eaten daily, but only with the morning or midday meals. (7) Raw vegetables, such as lettuce and other salads, are dangerous. Shell fish and crustaceans (with the exception of well cooked prawns) are unwholesome, while pork and ducks as a rule are wisely avoided by tropical residents.”

So far as the influence of exercise upon the development of this disease is concerned, Brown is of the opinion that exercise becomes a fad with many Europeans, especially the English, while residing in tropical countries and that it is frequently overdone. He states that fatigue is often unwisely mistaken for exercise, and he says that the smaller percentage of cases of sprue is furnished by the class who take exercise in strict moderation. He thinks that housing conditions among whites in India and other tropical countries have not been improved in recent years and that supplanting roomy, thatch covered bungalows with wide verandas, by modern European houses, has not improved health conditions in the tropics.

Students of sprue generally state that when the disease is recognized in a white resident in the tropics, immediate return home is a *sine qua non* if recovery is to be secured. Brown agrees that return home or leaving the tropics is desirable if the disease is detected or if the return is to be effected in the early state of the disease, but he says that peo-

ple with advanced sprue often go to their graves instead of to their homes when they make the attempt to do the latter under disadvantageous conditions. Bertrand and Fontan, observing sprue in Cochin China, say: "Let there be no parley with the disease; return home is absolutely necessary." Many Europeans developing sprue in Java and India seek to better their condition by a temporary sojourn at some hill station. On this point, Van der Burg says: "Removal to the uplands always does more harm than good."

While a book on epidemiology should, so far as possible, avoid discussion of treatment, it is only proper to say in this connection that no drug has been found to be of benefit in the treatment of sprue. Although so eminent an authority as Brunton did, for a while, have some confidence in preparations of bismuth and in *cannabis indica* in its treatment as he saw it in London among patients returned from tropical countries, further investigation has demonstrated the worthlessness of these preparations. For a time *santonin* had a run in the treatment of sprue, but Ashford has demonstrated that it is without value. The only successful treatment is dietetic and each expert has his own formula. Some employ an exclusive milk diet, but the milk should be uncontaminated and up to standard in its essential constituents, and such milk is not easily obtained in all parts of the tropics. Some physicians put their patients on a diet consisting wholly of fruits. Quite naturally, these fruits must be fresh and are tropical and include bananas, pineapples, strawberries, blackberries, alligator pears, mangoes, and others. Sometimes a mixed diet of native fruits and preserved milk is employed, while in still other cases an exclusive meat diet seems to give good results.

Bibliography

- ASHFORD, B. K.: *Jour. Am. Med. Assn.*, 1915, lxiv, 1893; *Am. Jour. Trop. Dis.*, 1915-1916, iii, 32; *Am. Jour. Med. Sc.*, 1916, cli, 528; *Rep. and Collect. Stud. Inst. Trop. Med.*, Porto Rico, San Juan, 1917, i, 49, 61, 73.
- BOYD, M. L.: *South. Med. Jour.*, 1920, xiii, 229.
- BROWN, W. C.: *Sprue and its Treatment*, London, 1908, John Bale, Sons and Daniels-son.
- DOLD, H.: *China Med. Jour.*, 1917, xxxi, 387.
- GRANT, A.: *Indian Ann. Med. Sc.*, 1854, i.
- HEATON, T.: *Indian Jour. Med. Research*, 1920, vii, 810.
- HILLARY, WILLIAM: *Observations on the Changes of the Air and Their Concomitant Epidemical Diseases in the Island of Barbados*.
- MANSON, P.: *Tropical Diseases*, New York, 1911, William Wood & Company.
- MICHEL, C.: *Jour. Infect. Dis.*, 1918, xxii, 53.
- THIN, G.: *Psilosis or Sprue: Its Nature and Treatment*, London, 1897, J. & A. Churchill.
- WOOD, E. J.: *Trans. Assn. Am. Physicians*, 1915, xxx, 505.

CHAPTER XV

MALTA FEVER

Mediterranean Fever; Undulant Fever

Description.—This is a continued fever, running usually from three to ten weeks, often much longer, and furnishing an irregular, undulating curve, with many exacerbations and remissions. It is caused by a specific microorganism, discovered by Bruce in 1889 and designated as *Micrococcus melitensis*. The designation as Malta fever is unfortunate, because, as we shall see, the disease has a world-wide range. The term undulant fever is much more suitable and expresses one of the marked characteristics of the disease. This disease is plainly differentiated from all other diseases etiologically, symptomatically, and pathologically. So far as its symptomatology is concerned, its most characteristic feature is its long continuation and the irregular exacerbations and recessions. The death rate is low, generally not exceeding 2.5 per cent. There are no cutaneous eruptions characteristic of the disease and whatever of these may be seen in individual cases is incidental and not due to the specific virus. Rheumatic and neuralgic pains are frequent accompaniments and sequelae. In a small, but notable, percentage of cases orchitis appears as a complication. The most constant pathologic change found after death, lies in the spleen, the size of which is markedly increased and the density of which is markedly diminished. There is no regularity or periodicity in the remissions. The temperature runs fairly high, sometimes reaching 105° or 106°, then declines for an indefinite period, when rather suddenly and without apparent cause it approximates, reaches, and possibly exceeds the preceding crest. During the remissions the patient's general well-being improves and he fancies that he has reached the final termination of his disease and great disappointment, accompanied by marked general depression, results from the exacerbation. During the exacerbations there is often profuse perspiration. The amount of water leaving the body through the skin is probably not exceeded in any other disease.

History.—The epidemiologist does not go far in his studies before he meets with strong evidence of the immutability of the epidemic diseases. Generally speaking, they run true to type throughout their recorded history, be this short or long. Tubercle bacilli found in Egyptian mummies are easily recognized by tests applied for the recognition of their kind taken from the sputum of the consumptive of today. The gradual

progress of pulmonary tuberculosis, its characteristic hectic flush, its gradual wasting of tissue, its harassing cough, and its certain termination in death, have been matters of common observation from the earliest historical times down to the present day. The characteristic symptoms and lesions of smallpox observed and described by Indian writers before the Christian era show no essential variation from those which manifest themselves in the unprotected individual of today. Then, as now, one attack of this disease gave, as a rule, protection against subsequent exposures to the virus. Ancient Hindoos practiced inoculation in this disease and the symptoms induced and the results secured were identical with those observed many centuries later, when this method of mitigating the severity of the disease was practiced in western Europe and in America. Practically the same phenomena, in the same order, have appeared in every child vaccinated with cowpox that were seen and described by Jenner in his experiments on the Phipps boy in 1796. It follows that through all these centuries there has been no important mutation in the smallpox virus, nor any marked modification in its behavior when introduced into the human body. The most ancient descriptions of the plague are so plainly indicative of the disease as we have known it in the present generation, that there can be no mistake of the identity of the virus of this disease in most ancient times with that of the present. The pneumonias of today are marked by the same seasonal variations, characterized by the same modes of onset, by like avenues of progress, and by similar results with those seen and described by Hippocrates. The description of mumps, with its accompanying orchitis, given by the great Greek physician more than 2,300 years ago, might have been written by any intelligent observer yesterday. The differentiation between smallpox and chickenpox and between scarlet fever and measles made by Arabian physicians of the ninth and tenth centuries holds good today. Because bacteria and protozoa are low forms of life, it has been assumed that they are especially liable to marked mutations, involving alterations in chemical composition, and, what is of more importance so far as pathogenic organisms are concerned, in their effects upon man. In our opinion, this assumption is not warranted by any facts which can be gathered in a study of the history of disease. The pathogenic viruses, so far as their history is revealed by a study of their effects upon man, have undergone no radical mutation, certainly not in function, within the centuries covered by human record. There may be new diseases developing from time to time. We have no data which would justify a negation of this, but, so far as historical evidence gives us information, we may say that the so-called discovery of new diseases has resulted from a differentiation of dis-

eases. Cerebrospinal meningitis, as first recognized in Geneva in 1806, is not due to a newborn organism of about that time but had existed for centuries and was confounded with typhus fever. This is true of the recognition of typhoid fever, made possible by the autopsy studies of French and American physicians early in the nineteenth century. The greatest progress in medicine has been through correct diagnosis and improvement along this line has followed the extension of pathologic, chemical, and biologic methods. Observation of symptoms alone was sufficient to enable Greek physicians to distinguish between types of malaria, and it may be added here that the effects of the different varieties of plasmodia on man show the same differences today as they did 2,300 years ago. Malaria in the Attic Plain of Greece is the same today as it was at the time of Aristophanes.

The epidemiologist is struck with another important fact. The diseases of a given region have remained very much the same through all history, except when the conditions of life are modified by man. We have taken occasion elsewhere to call attention to the fact that some of the most successful campaigns against disease have resulted incidentally and without man's being conscious of the fact that his doings would in any way improve the health of his kind or prolong life. The ancient Romans, when at great expense and labor they introduced abundant and pure water-supplies into Rome, so far as we know, had no idea that they were improving the health conditions of the city. They were led to do these things solely by their esthetic sense and from a desire to make their own lives more comfortable and more luxurious. They delighted in baths and in the play of fountains. Large areas of malarial lands have been rendered healthful habitations by clearing the vegetation and by drainage, but in many instances these works have not been done with the idea of the abatement of malaria but for the purpose of reclaiming the soil and making it more productive. The discovery of glass and its utilization in windows have been of undoubted service in decreasing the prevalence of malaria. Unlighted houses formed ideal places for the assembling of anopheles. It is only within recent years that man has undertaken important works with the direct object and intention of combating disease. The intelligent reader will understand that some of man's attempts to improve his local conditions as a means of increasing his health, have, temporarily at least, favored the extension and progress of disease. The rapid development of the manufacture of paper in New England in the eighties of the last century led to the building of dams for water power and for a while numerous mill ponds, even in the Berkshires, became breeding-places for anopheles and led to the recrudescence of malaria in that region. The disposition of fecal matter

by water carriage and the discharge of untreated sewage into streams from which cities and villages took their drinking water led for a time to an increase in the prevalence of, and the death rate from, typhoid fever.

We have been led to make the remarks recorded in the above paragraphs by the fact that undulant fever, the subject of discussion in this chapter, is an illustration of the long continuation of a specific disease in a given region. That this disease not only existed in ancient Greece, but was described by Hippocrates, there can be no doubt. In his work on epidemics, the father of medicine describes a protracted fever which did continue, in some instances, as long as 120 days and which was marked by the exacerbations and remissions characteristic of the disease. He says:

“Apyrexia at times, at others not; for if the fever intermitted and was alleviated for a little it immediately relapsed again.”

Here we have an illustration of the long continuance of a specific disease in a given geographical area. Through the centuries when civilizations were born, grew into maturity, fell into senility and were replaced by succeeding civilizations—during all these ages, specific diseases, of which the one now under discussion is only an example, prevailed among the inhabitants, whether civilized, semi-civilized or barbarian. Phœnician, Carthaginian, Greek, Roman, and lesser civilizations, had their little days in this region, but during all this time certain specific diseases went on, apparently in their uninterrupted course. It seems that Adams, translator of the works of Hippocrates, had this impression made upon him, for he wrote:

“The conclusions to which a patient study of modern authorities on the subject have brought me, amount to this, that the fevers described by Hippocrates in his epidemics are exactly the same as those which are now described as still prevailing in the land of Greece; and that they correspond very well with those described by Cleghorn as occurring in Minorca.”

Veale, writing of the fevers of the Mediterranean in 1881 and giving special attention to that form which we are now discussing, thinks that, making allowance for differences in modes of thought and expression at the time of Hippocrates, his writings contain what “might almost pass for a brief description of this disease.”

From the time of Hippocrates down to the eighteenth century there is, so far as we know, no description of Mediterranean fevers in which there is anything sufficiently definite to apply to what is now known as Malta fever. During the eighteenth century there is an occasional mention of the prevalence of a simple, long continued fever in the wards of the great hospital of the Knights of St. John on the Island of Malta,

and in 1751 Cleghorn wrote his now classical monograph on the fevers of Minorea, in which he tells of the prevalence of an irregular, incurable and continued fever, marked by relapse after relapse and accompanied by excessive perspiration and upon which Jesuits' bark had no effect. In reporting an autopsy from this disease and speaking of the spleen, he says that this organ was

"so excessively soft and rotten, that it had more the appearance of congealed blood wrapped in a membrane than of the original part."

It may be interesting to read extracts from two authorities on the hospital of St. John of Jerusalem on the Island of Malta as it was in the palmy days of the reign of that Order. The first extract is from the work of Howard, the philanthropist, on the Lazarettos in Europe. After saying that the food was served the patients from silver bowls, this author adds:

"The number of patients in this hospital during the time I was at Malta (March 29 to April 19, 1786) was from five hundred and ten, to five hundred and thirty-two. These were served by the most dirty, ragged, unfeeling and *inhuman* persons I ever saw. I once found eight or nine of them highly entertained with a delirious *dying* patient. The governor told me they had only twenty-two servants, and that many of *them* were debtors or criminals, who had fled thither for refuge. At the same time I observed that near *forty* attendants were kept to take care of about twenty-six *horses* and the same number of *mules*, in the grand master's stables; and that *there* all was clean. I cannot help add, that in the center of each of these stables, there was a fountain out of which water was constantly running into a stone basin; but that in the hospital, though there was indeed a place for a fountain, there was no water. * * * The slow hospital fever (the inevitable consequence of closeness, uncleanness and dirt) prevails here."

The second extract is from Boissgelin, himself a Knight, in his work on Ancient and Modern Malta, in which he writes concerning the hospital, as follows:

"The hospital consists of several large airy apartments, and of immense storehouses, which would contain four times the number of beds at present employed. This asylum is constantly open for the reception of the sick of all countries and religions; who are treated with every possible attention; and furnished with medicines and comforts of every kind. The Knights not only inspect the different branches of the administration (the head of which is one of the first dignitaries of the Order), but successively attend the sick, of whom more than 2,000 are annually discharged cured from the hospital. The utensils employed are almost all silver; but of such plain workmanship as sufficiently proves that this magnificence was adopted from a motive of cleanliness, and not as an object of luxury."

After the English occupation of Malta (1800) a vast volume of literature on fevers prevalent on the Islands and Coasts of the Mediterranean began to appear. Through all of these contributions it is evident that the specific fever now known as Malta fever was prevalent throughout the Mediterranean region. Marston, who was stationed on the Island of Malta for a period covering the Crimean War, was the first to differ-

entiate what is now known as Malta fever from other fevers seen at Malta and at other places on the Mediterranean Coast. Marston's paper is full of interest all the way through. He clearly differentiates between typhus and typhoid fevers. In his opinion concerning the causation of typhoid, he seems to have been a somewhat reluctant disciple of Budd, who at that time was teaching the specific and contagious nature of this disease. While Marston was inclined to follow the teaching of Budd, he reserved the belief that typhoid fever might, under certain circumstances, originate spontaneously or *de novo*. However, our present purpose is not to discuss typhoid fever, but to ascertain what Marston said concerning what is now known as Malta fever. He discussed this disease under the names of Mediterranean remittent and gastric remittent fever. He wrote in part as follows:

"By this is meant a fever characterized by the following symptoms and course: A preliminary stage of subacute dyspepsia, anorexia, nausea, headache, feeling of weakness, lassitude, an inaptitude for exertion, mental or physical, chills, muscular pains; lastly, a fever, having a very long course—three to five, or ten weeks—marked by irregular exacerbations and remissions, great derangement of the assimilative organs, tenderness in epigastric region, splenic enlargement, slight jaundice, without any exanthem. Neither bronchitis nor diarrhea, as a rule. The patient is prone to relapses, and the disorder is followed by a protracted convalescence and a chloroanemic aspect. Very frequently also by rheumatism of some form or other, but without any tendency to lesion of the peri- or endocardial membranes. Pathologically, it is marked by congestion or inflammation, with softening of the enteric mucous membrane, (particularly that of the stomach and duodenum), without any lesion of the Peyerian follicles, but with hypertrophies of the liver and spleen.

"There is no fever so irregular as this in its course and symptoms. The disease prevails particularly during the spring and summer months, (less so, during the autumnal period of the year), and, generally, during years in which the typhoid form is in abeyance. It replaces, and is in turn replaced by that fever (typhoid), and, sometimes occurs concurrently with it.

"The natives of the place are affected in a much less degree than those temporarily residing here; and, of these latter, the older residents appear to evince the greatest proclivity to the disease.

"It affects, *par excellence*, young men, under thirty-five, particularly those of rheumatic diathesis; next in frequency children; most infrequently, the aged. To enter into the description of its symptoms more in detail:—There is invariably a preceding stage of dyspepsia, of indefinite duration, irregular bowels, acid eructations; disinclination for food, lowness of spirits and restlessness at night. Upon this state pyrexial symptoms supervene, sometimes suddenly, so as to resemble an attack of intermittent, and the patient seeks the hospital. The febrile symptoms are particularly prone to remissions of an irregular type. Almost invariably there is a nocturnal exacerbation, ending in diaphoresis—often profuse. The pulse, rarely below 80, often reaches 120, soft and voluminous. The dyspeptic symptoms are well marked—vomiting or nausea is generally present; pain, three to four hours after eating, referred to the esophagus and stomach; invariably anorexia. The patient hawks up, in the morning, quantities of mucus, occasionally mixed with a little blood. This appears to come from the pharynx. Hematemesis is rare. The tongue is large, flabby, with slightly reddened

periphery, and covered with a whitish-yellow, or a very thin semi-opaque fur. What rarely happens in pyrexial diseases, the tongue in this is sometimes sodden and marked, laterally, by impressions of the teeth. It becomes glazed during the progress of the disorder. The tonsils are generally slightly congested, and their follicles prominent. A diseased state of the *velum palati* is often present. This part is relaxed and congested, and sometimes presents numerous minute opaline spots (aphthae), or a thin, translucent, whitish exudation, which peels off, leaving a glazed reddened surface. A similar coating is occasionally found upon the gums, which then look spongy and project between the neighboring teeth. Sometimes an appearance not unlike that of stomatitis ulcerosa appears. A highly intelligent military surgeon conceived, from the appearance of the gums in some cases, that a scorbutic condition of blood was present, and prescribed accordingly, without the least benefit however. The semi-opaque fur becomes a favorite nidus for the development of vegetable germs (the *oidium albicans*). The saliva has generally an acid reaction to litmus.''

At autopsy, Marston found the most common abnormality consists of an enlarged spleen, the parenchyma of which is softened and engorged with extravasated blood. This author has given a lucid description of a mild attack of Malta fever, from which he himself suffered. During the Crimean War, Malta was used as a depot for troops, both going to and coming from the war area. Quite naturally, at this time the hospitals on the Island were filled with those suffering from the various diseases acquired either in their home country or in the war zone. Among the febrile cases there were many of the disease which we are now discussing, and some have suggested that this specific disease was first brought to the Island of Malta at that time. Marston and others have shown that this view is unfounded and that the disease had existed on the Island and in other islands and on the shores of the Mediterranean from time immemorial. Before, and for some time after Marston's clear demonstration that this is a specific disease, it was confounded on the one hand with malarial fevers, from which it should be easily distinguished by the irregularities in its intermissions, and on the other hand with typhoid fever, from which it differs markedly in mode of onset, progress of symptoms, duration, and fatality, to say nothing of the very clear and constant differences in postmortem findings. In 1879 Veale, studying the symptoms and making autopsies of febrile soldiers invalided home from Mediterranean stations, confirmed Marston's claims and made even clearer distinctions between undulant fever on the one hand and malarial and typhoid fevers on the other. It may be said that Veale fully established the specificity of this disease from a study of its symptomatology and pathology. It remained, however, to discover its specific cause. In the same year that Veale's paper appeared, Fazio, under the name of Neapolitan fever, described in detail the nature of the disease and pointed to the probability that it would be found to be due to some specific microorganism.

Veale's article, founded upon a study of the clinical symptoms and postmortem findings in a hospital in England receiving invalided soldiers from Mediterranean ports, so forcibly illustrates the value of close observation in the differentiation of diseases at a time when we knew but little concerning pathogenic bacteria that we are led to make a further reference to his work. In the English hospital among the invalided soldiers, this medical man had to deal with typhus, typhoid, malaria, remitting fevers and others, some of which could not be classified. After making these studies and detailing his observations, Veale came to the conclusion that he had among his patients cases of not only well-known and typical fevers, but some suffering from a specific disease not at that time clearly recognized. He then asked himself what can be the cause and what the nature of this disease. We quote:

“What then is its cause and what is its nature? To these questions the answers can as yet be only negative. That it is not our enteric fever appears certain, from the fact that it has neither its clinical form, nor its mortality, nor its specific anatomical lesion; that it is not a malarial fever seems proved by its absolute resistance to quinin, by its protracted duration after removal of the sufferers from a malarial locality, as well as by its different aspect and progress throughout; that it is not relapsing fever may be concluded from the positive facts that it is neither epidemic nor contagious, and that it has a different mode of invasion as well as of evolution, and from the negative fact that no spirilla have hitherto been found in the blood during the periods of relapse; and that it is not dengue, any one, I think, may satisfy himself by perusing a description of the latter disease. It certainly has very little resemblance to the dengue that I have seen.”

In 1886 Bruce began on the Island of Malta his bacteriologic studies of this disease which have led not only to the discovery of the specific organism and the avenues by which it is transmitted, but have placed in the hands of medical men in all parts of the world the methods by which it can be positively and scientifically diagnosed and differentiated from other diseases. In the spleen of a patient who died on the fifteenth day of the disease, Bruce found enormous numbers of single micrococci scattered through the tissue. Even when not permitted to make an autopsy he succeeded in withdrawing some of the spleen pulp through a sterilized trocar and demonstrated the organism in the tissue thus secured. Later he found that he could cultivate this organism on agar. Monkeys inoculated with pure cultures developed the disease, which, in these animals, runs a course quite similar to that observed in man. In one monkey the fever, with the characteristic irregular waves, persisted for 94 days, after which the animal completely recovered and lived in good health for three years, when it was killed by a dog. Some of the monkeys died, and in these the pathologic conditions and the distribution of the microorganisms were found to be much the same as they are in man. It has been shown experimentally that goats, cows, horses,

asses, and fowls may carry the organism for long periods of time without suffering recognizably therefrom.

Present Distribution.—Armed by Bruce's discoveries, with the procedures necessary to make a positive diagnosis, physicians in various parts of the world have demonstrated the wide distribution of this disease. It has been found on all the Mediterranean Islands and in all countries bordering upon this Sea. On the mainland it has been found not only at seaports, but in regions far inland; at least, this has been found to be true in France, Spain, Italy, Greece, Egypt, Tripoli and Algeria. There are endemic areas in northern India and in China. Craig and other American Army officers have recognized it in the Philippines, and it is probable that many United States soldiers carrying this infection have been invalided home. In Africa it became highly prevalent on the Cape, in the Transvaal, and in the Orange Free State, following the Boer War. In northern Africa there are endemic centers in the Sudan, in Uganda, along the Blue Nile and about Lake Chad. In the United States there is an endemic area, probably of considerable antiquity, in Texas, extending into New Mexico. It will, of course, be understood that Malta fever may be seen at all seaports receiving passengers from endemic centers, but we are now discussing those areas in which the disease is indigenous. In 1905 Craig reported a case of this fever in a nurse in a hospital in Washington. It was thought that she became infected in taking care of soldiers from the Philippines. In the same paper, this author reports nine cases of the disease in soldiers who became infected in the Philippines. Some years later Ferenbaugh, stationed at Del Rio, Texas, reported five cases among persons engaged in the goat raising industry along the Pecos River. Further cases in the same region were reported by Ferenbaugh and Gentry. Texas, New Mexico, and Arizona are the chief goat raising states in the Union, and the flocks of this animal have been replenished from time to time by importations from Malta and other Mediterranean ports. Mohler and Eichhorn, of the U. S. Bureau of Animal Industry, state that in 1905 the Department of Agriculture brought goats from the Island of Malta to this country for the purpose of establishing a goat-milk industry. On examination, many of these animals were found to carry the *Micrococcus melitensis* and, as a result of this discovery, the imported goats and their offspring so far as possible were destroyed. However, that was not the first time that goats from Mediterranean ports had been brought into the United States, and it is more than probable that in 1905 undulant fever had been planted in more than one part of the United States. In 1911 Ferenbaugh and Gentry found that 34.7 per cent of the goats examined by them at Langtry, Texas, gave the agglutination test with

the *Micrococcus melitensis*. According to Yount, the State Board of Health of Arizona, issued a circular on Malta fever in 1912, in which the following precautions were advised:

“(1) All goat's milk should be boiled or brought to the boiling point before it is used for drinking purposes, on cereals, or in coffee. (2) All goat corrals or bedding grounds, should be located at a distance from the residence. (3) Avoid sleeping in or near goat corrals. (4) After handling goats always wash the hands well with soap and water before eating.”

Bassett-Smith states:

“In Texas and New Mexico the disease has been known as mountain or ‘slow fever’ for at least 25 years, and is always found among people employed in goat rearing, the cases being most common after the kidding season during April, May and June.”

The *Micrococcus*.—*Micrococcus melitensis* generally appears as a typical coccus, though it may be elongated, justifying the designation of a cocco-bacillus. Branching forms or bacillary forms are quite numerous on certain culture media, and Hiss and Zinsser believe that they are justified in naming this organism *Bacillus melitensis*. Diplococci and streptococcic chains are frequently seen. The organism grows well on slightly alkaline media kept at a temperature of from 37° to 38° C. Between 40° and 42° C. growth is arrested, and above 42° C. the organism dies. The temperature range of growth outside the animal body runs from 15° to 42° C.

For the purpose of securing agglutinating sera, rabbits are treated with subcutaneous inoculations of living cultures. From three to six, sometimes more, such inoculations are given at intervals of from three to five days. After such a course of treatment the sera of these animals are found to agglutinate cultures of *M. melitensis* in dilutions of from 1-60 to 1-2000. So far as we know, high agglutinating sera (1-2000) are but rarely obtained. Sera thus prepared are used for diagnostic purposes and for the differentiation between strains of this organism, of which at least five are now recognized. One of these strains is known as *M. paramelitensis*, while others have no distinctive names and are distinguished only by numbers. In 1912 Nègre and Ranaud described a *M. pseudomelitensis*, which can be differentiated from the strains of the true organism by agglutination and absorption tests. These agglutinating tests may be applied to the sera of the sick for diagnostic purposes and to either the milk or the sera of goats and cows in order to ascertain whether or not these animals bear the infection. Bassett-Smith gives the following points to be observed in the preparation and use of these sera:

“(1) The culture to be used should be proved to be active with known specific sera and should not agglutinate with other sera. The use of a *paramelitensis* strain would fail to agglutinate in high dilutions with a true undulant fever serum and give rise to a

negative error. (2) As recommended by Nègre and Ranaud, heated and untreated serum should be tested, the former cutting out the nonspecific agglutinins and preventing a positive error in nonundulant cases. (3) The test should always be carried to high dilutions, up to 1 in 400, to avoid paradoxical reaction."

In making a diagnosis of this disease in man, the best method is to draw, under aseptic precautions, from one to five c.c. of blood and distribute this in two flasks of nutrient broth. After incubation, subcultures should be made on agar. Three days later good growths may be obtained and employed with a specific serum in making the agglutination tests. It will be understood that a control test with normal blood and the specific serum should always be employed. As is done in the agglutination test for typhoid fever, emulsions of the micrococcus killed with formalin may be kept in stock and employed in the place of fresh cultures. Bassett-Smith has used the agglutination test in cases of undulant fever in normal individuals and in those suffering from other diseases. Out of 65 control sera, tested with five strains of *M. melitensis*, there was only one positive reaction. Out of 150 sera from patients, in a naval hospital, suffering from a variety of diseases, four gave a positive test, and it was found that these had been previously under treatment for a fever at a Malta hospital. In determining the presence of this disease in cows and goats, reliance is generally placed upon the lacto-reaction or the agglutination of milk with a specific germ. Employing this test on the goats of Malta in 1912, Zammit found that fifty per cent of them carried the infection. In the same year, Nicolle found thirty per cent of the milch goats of Tunis infected and Coner and Huon, thirty-four per cent in Marseilles, while Sergent found only 3.4 per cent infected in the Algerian herds.

The micrococcus in infected men and animals appears to be largely eliminated through the urine. In some instances this excretion furnishes a pure culture and the organism may be obtained by spreading a few drops of the urine on agar and incubating. Although this is sometimes used as a diagnostic test, a negative result does not exclude the possibility of the existence of the disease. Elimination of the organism through the urine permits a single infected animal when added to an uninfected herd to pollute the pasturage upon which the animals feed. It should be understood that animals carrying this infection usually appear to be quite healthy and, indeed, there is no positive proof that this micrococcus is accountable for any disease in goats, although it has been observed by Nègre that infected herds show an unusually large proportion of cases of chronic mastitis.

Transmission.—It is probably true that no parts of the earth's crust have been so long, so continuously, and so abundantly polluted and so heavily saturated with the excretions of man and animals as certain

Mediterranean stations. Take the Island of Malta for instance, the station which gives its name to this disease, and history shows its occupation by all kinds and conditions of people from the earliest historical time, and even beyond that tradition points to a like occupation extending backward through unknown centuries. The Knights of St. John occupied Malta from 1530 to 1798. Some of the buildings they constructed were used as barracks and hospitals when Marston collected within their walls the data which enabled him to show that he was dealing with a specific disease. After the specificity of the disease had been demonstrated it was quite natural to conclude that it had its cause and originated in the grossly insanitary condition of the Island. It was believed that in order to exterminate the disease it would be necessary to remove, so far as possible, the accumulations of filth from the soil, water and air, or, at least to prevent the further pollution of these essential environments of life. English sanitarians went to work, constructed sewers, brought in pure water-supplies, and drained the small marsh areas which bordered some of the harbors. The conditions, not only of soldiers and sailors in garrison, but of the civil population of the Island, were greatly improved. Typhoid fever was greatly reduced both in incidence and in death rate, but improved sanitation apparently had no effect upon undulant fever; indeed, the first steps in the improvement of the sanitation of the Island were accompanied and followed by an increase in the prevalence of Malta fever. This was true not only on the Island of Malta, but at other Mediterranean ports. In 1899 Bruce wrote the following:

“It is curious that the introduction of the system of removal of excreta by sewers has been looked upon, rightly or wrongly, as coinciding with an excessive development of this fever in Valetta, Naples and Catania. Eugenio Fazio, in writing of the Neapolitan fever, states that from the time the old-fashioned emptying of cesspools was suppressed and the house drains were carried into the main sewers, which had previously been used for the carrying off of rain water, the hygienic condition of Naples was changed. The fecal materials being collected in a cloacal system which was not well constructed—being not only deficient in downfall, but also in water for flushing—there stagnate and infiltrate the subsoil, especially as this is a porous rock, whence are poured into the atmosphere the products of putrid fermentations.

“Tomaselli writes in the same manner concerning the fever in Catania. He states that its occurrence and causation seemed to have some connection with local sanitary conditions, which had been modified by the introduction into the public streets of the sewer system, and the first outbreak corresponded in fact with the epoch of this reform. In his opinion the immense quantity of the results of decomposing organic matter which is developed in these sewers, and finds its way out, must be placed in the front rank of causation. He is certain that, under the existing circumstances in which there is scarcity of water for flushing purposes, the city of Catania lies under the malign influence of a poisonous miasma, which is continually given off from these subterranean sources. In like manner it was fashionable in 1886 in Valetta, Malta, to blame the

introduction of a general system of drainage for the great increase in the number of cases of this fever during the two years in which the system had been in operation. Among the soldiers this increase had certainly been very marked. And as it appears that the sewers were in operation before an efficient method of flushing was introduced, Tomaselli's words in regard to Catania may have been applied to Valetta. Since 1886, due mainly to the energy of Sir Walter Hely Hutchinson, the Lieutenant-Governor, the hygienic condition of Valetta has much improved.'

As late as 1897, Hughes, in the most exhaustive monograph on this disease ever published, and ten years after the discovery of the micro-organism, summed up the studies as to its causation, as follows:

"So far we have arrived at the conclusion that there are reasons for believing that undulant fever is caused, in the majority of instances, by a specific micrococcus emanating, during hot dry weather, from a saprophytic existence in soil polluted with the feces of those suffering from the same disease. From the fact that the infection apparently travels through the air, and that the initial symptoms are, as has been recently noticed in certain other diseases, tightness in the throat, redness and tenderness of the tonsils with often a coating of translucent fur, a furred tongue, slight swelling of submaxillary and cervical lymphatic glands, epigastric tenderness, anorexia, nausea, and even vomiting, pain and stiffness of the muscles of the neck and back, it is not unlikely that the virus gains entrance to the human body by means of the inspired air.'

The natural reservoir which contains the *Micrococcus melitensis* remained unknown until 1905, when the War Office, Admiralty and the Civil Government of Malta appointed a commission, consisting of Kennedy, Zammit, and Horrocks, to study this disease and to ascertain the path of transmission. This Commission made the following highly important discoveries: (1) The micrococcus is largely eliminated from the body in the urine. (2) It is capable, when the temperature limits are not unfavorable, of continuing its existence for long periods extracorporeally. (3) The milk of many goats agglutinates cultures of *Micrococcus melitensis*. (4) About fifty per cent of the milch goats on the Island of Malta carry the micrococcus and eliminate it in their milk. (5) Monkeys and susceptible men fed on milk from infected goats developed the disease after a period of incubation of 14 or 15 days. (6) A goat carrying this organism in its blood and eliminating it in its milk may remain in apparent health and continue the elimination of infected milk quite indefinitely. (7) An infected goat introduced into an uninfected herd may infect others.

It should be understood that the goat is not the only milk-supplying animal which may carry and distribute the infection, although, so far as we know at present, the goat is more liable to this infection than any other mammal. Cows, mares, and asses are known to be susceptible to the infection and to eliminate the specific micrococcus in their lacteal secretions. By means of the lacto-reaction, cows in endemic areas have frequently been found to be infected. Although Kennedy obtained

positive reactions in three out of 22 cows examined in London, the wider investigation by Bassett-Smith justifies the conclusion, at least until further experimental work is done, that the milch cows of England do not bear this infection and, so far as we know, this is true in the United States and Canada.

Control.—From what has been said, it is evident that the primary essential for the eradication of this disease in endemic areas is to see that no unsterilized goat's milk is used. There are, however, other ways by means of which infection may be transferred from infected animals to man. Bassett-Smith says:

“As in typhoid, one must look to the three F's—food, fingers, and flies—as possible carriers of the organism.”

Bibliography

BASSETT-SMITH, P. W.: Jour. Roy. Naval Med. Service, 1915, i, 166.

BOISGELIN, L.: Ancient and Modern Malta, London, 1805, Richard Phillips.

BRUCE, D.: Practitioner, 1888, xl, 241; British Med. Jour., 1889, i, 1101; Army Med. Report, xxxii, 365.

HOWARD, J.: Lazarettos in Europe, London, 1789, Cadell, Johnson, Dilly & Taylor.

HUGHES, L.: Mediterranean, Malta Undulant Fever, London, 1897, Macmillan Company.

MARSTON, J. A.: British Army Med. Reports for the Year 1861, p. 486.

VEALE, H.: Army Med. Report (British), xxi, 260.

YOUNT, C. E.: Mil. Surgeon, 1913, xxxiii, 540.

CHAPTER XVI

SOME TREMATODE INFESTATIONS

I. The Schistosomiasis

Urinary Schistosomiasis.—Under the designation of schistosomiasis we include a group of diseases differing more or less markedly in symptomatology, pathology, and geographical distribution, but all due to closely related trematodes belonging to the order of Schistosomatidae. It is a question as to how these diseases should be classified. This may be done according to the species of the parasite or with reference to the symptoms, or by taking into account the geographical distribution. We have chosen a classification determined upon by the part of the body most seriously and most frequently involved, and upon symptomatology. It is a fact well known through all historical time that hematuria was frequent among the Egyptians, and Ruffer has demonstrated the presence of calcified eggs of the parasite, which we now know causes this hematuria, in mummies of 1250 to 1000 B.C. During the Napoleonic campaign in Egypt (1799-1801) hematuria was a frequent manifestation among the French soldiers. The cause of this urinary hemorrhage was first determined by Bilharz who, in 1851, discovered in the bladders and in the urine of infected persons the eggs of a trematode worm. In 1859 Cobbold named this worm "bilharzia," and for many years the disease was known as bilharzia disease or Egyptian endemic hematuria. It was found, however, that Weinland had some years before Cobbold proposed this name, designated this genus as *Schistosoma*, and consequently the name of the disease has been changed to schistosomiasis.

In recent years this disease has been found widely distributed over northern and central Africa and endemic in some of the more southern areas of that continent. It is, however, best known and probably most abundant in Egypt, Tunis, Algiers, and Morocco. It is found in Asia Minor, Persia, Mesopotamia, and Palestine. It has been reported in the islands off the eastern coast of Africa and in some of those of the Mediterranean. Occasional cases have been reported from the Western Hemisphere, especially from the West Indies, though more rarely from both North and South America, and still more rarely over central Europe. Whether these cases are identical with the endemic hematuria of Egypt and other portions of Africa must be regarded as not certainly determined. This is also true of the reports of the presence of the dis-

ease in Australia. The most characteristic symptom of this disease is a hemorrhagic cystitis, which comes on gradually and increases in severity. Early in the development of the disease there is usually only a small amount of blood eliminated with the last drops of urine. As the disease progresses the whole bulk of the urine may be highly colored with blood, may contain small clots and heavy blood-stained deposits may form on standing. Pain is not always marked and with the exception of frequency of micturition, a little scalding and some straining, the symptoms may not be severe and may continue in this way for months and even for years. In other instances the severity of the cystitis becomes intensified more rapidly. The urine, at first clear and acid, undergoes decomposition in the bladder and is eliminated with an ammoniacal reaction. Gravel and stone may be formed in the bladder or in the pelvis of the kidney. The mucous surface of the bladder becomes engrossed with deposits of phosphates only or of phosphates mixed with oxalates or uric acid. The walls of the bladder are thickened and abnormal growths in these tissues sometimes develop. The ureters may become clogged, leading to stagnation of the urine, backward pressure, dilatation of the pelvis, and structural disease of the kidney. The bladder may be ruptured and urinary fistula, with openings above the pubes or in the perineum, may develop.

In the female, vaginitis and cervicitis may result. Stricture of the urethra, with all its discomforting complications, may arise. Finally, the patient falls into an anemic state and rapidly loses flesh, or septicemia develops and terminates in death. While the urinary system is most frequently involved in this form of schistosomiasis, there are instances in which the parasites accumulate in other parts of the body, blocking minute blood vessels and causing internal hemorrhage. There may be great accumulations of the ova in the lungs, and these may cause the development of pneumonia. In the brain or cord, such accumulations may result in paralytic symptoms.

The recognition of this disease is rendered easy by the demonstration under a low power microscope of the presence of the ova in urinary deposits. Fairley, by using an extract of infected snails, has prepared an antigen with which a test may be made after the Wassermann reaction. It is not likely, however, that this test will need to be widely employed, since the microscopic demonstration of the eggs in the urine is easy. Christopherson and McDonagh have shown that this form of schistosomiasis yields, with a fair degree of satisfaction, to the intravenous injection of tartar emetic. They begin with $\frac{1}{2}$ grain dissolved in 6 c.c. of sterile saline solution, and they state that by increasing the dose by $\frac{1}{2}$ grain every other day up to a maximum of $2\frac{1}{2}$ grains a dose

the parasite can be destroyed after from five to ten such doses. Emetin has been used by Diamantis by intramuscular injection, and this investigator claims that emetin is preferable to tartar emetic in children.

Intestinal Schistosomiasis.—In his original work on the endemic hematuria of Egypt (1851) Bilharz recognized the fact that while some of the ova of the parasite had terminal spines, others were laterally spined. In 1903 Manson suggested that the laterally spined eggs, which he first saw in examining a patient from the West Indies who had never visited Africa, might be indicative of a different species. This patient had had at no time any urinary trouble but had suffered from severe rectal ulcerations. It seems that urinary schistosomiasis is uncommon in certain localities in Africa, especially in the Congo Free State, and has never been seen in Porto Rico; while in these countries intestinal schistosomiasis is found. The symptoms in this form of the disease are such as would result from pathogenic changes in the rectum corresponding to the hemorrhagic cystitis of the urinary form. The symptoms are dysenteric, with the stools containing mucus and blood, accompanied by tenesmus and containing the characteristic laterally spined ova. Polypoid protrusions from the mucous membrane may fill the rectum and extend as high as the sigmoid flexure. The eggs are easily detected in the stools, and may be found in the urine as well. It is quite certain that in Egypt and in other parts of Africa the same individual may carry and may suffer from both of these varieties of the parasite.

Hepatic Schistosomiasis.—In 1887 Majima called attention to the fact that in a certain district in Japan, especially in the region of Katayama, there was occasionally seen a fatal disease of the liver, in which this organ was found to contain great numbers of the ova of some unknown parasite. On account of the locality in which it was first recognized and where it has continued to exist, this has been called the Katayama disease. In 1904 Katsurada ascertained that these eggs were those of a new species of *Schistoma*, which he called *Schistoma japonicum*. The most striking feature in this form of schistosomiasis is the marked enlargement of the liver and spleen. The former is nodular and when a bit of this tissue is digested in a three per cent solution of potash, the eggs of the parasite are left in great masses. It will be seen that this is a much graver disease than other forms of schistosomiasis. Fortunately, even in endemic areas it is not so frequently prevalent and, besides, in many cases it is slow in development. Manson-Bahr makes the following statement concerning the symptoms:

“The course of the disease can be divided into three stages. The first occurs within a short period of infestation and lasts about a month. It is associated with toxic symptoms, such as pyrexia, urticaria, abdominal pain, paroxysmal cough, and a high eosinophilia (sixty per cent or more). The second stage is characterized by great

emaciation and is accompanied by dysenteric symptoms and enlargement of the liver and spleen. The third or final stage, when it does supervene, occurs from three to five years after infestation. In this the liver is cirrhotic and enlarged. Ascites and edema of the extremities appear, with anemia and exacerbation of the dysenteric symptoms. The patient may die of exhaustion or of some terminal infection. Jacksonian fits, due to deposition of ova in the brain cortex and hemiplegia have been described."

The Parasites.—Adults of these parasites have their natural habitat in the portal circulation and it was here that Bilharz discovered them in 1851. The male is from 12 to 15 mm. in length and appears to be cylindrical. In truth, it is a thin, flat worm and the cylindrical form is brought about by approximating the margins ventrally, much as a man would fold a cloak about himself. This fold, leaving spaces where the margins do not touch, causes the appearance which fully justifies the scientific name, *Schistosoma* (a cleft body). This fold provides a partially closed canal, which is occupied by the female during copulation and is known as the gynecophoric canal. The surface of the male is covered with slightly elevated bosses or tubercles, which enable the parasite to cling to the walls of the blood vessels. The male carries both an oral and a ventricle sucker, which are close together. There are five testes which lie within the gynecophoric canal. The female is longer, about 20 mm., and much thinner, about .25 mm. Both males and females may be found, sometimes in great numbers, in the portal circulation. When the reproductive period approaches, the female enters the gynecophoric canal with both head and tail protruding, and the male, thus embracing his partner, traverses against the blood current the inferior mesenteric vein and continues his journey until he reaches the venules of the bladder. The decreasing diameter of the blood vessels forbids the further advance of the united pair. When this point is reached the female leaves the gynecophoric canal and, by virtue of her smaller size, she proceeds further along the blood vessels until limited in her progress by the diminishing size of the venule. Then she begins to deposit her eggs in the lumen of the vessel in front of her with a backward movement as she makes these deposits. The eggs are from .08 to .15 micron in length and from .04 to .06 micron in breadth. They are oval in shape and each carries a terminal spike, which aids it in piercing the wall of the blood vessel and finally reaching the interior of the bladder. As eliminated in the urine, the eggs contain ciliated embryos (miracidia). In water the egg swells, ruptures, and the miracidium swims about freely in search for a suitable snail and, having found such a host, the embryo enters and takes up its residence in the liver.

Manson-Bahr makes the following statement:

"The exact nature of the process by which the ova leave the body of the human host has been explained by Fairley and the Editor from observations upon experi-

mentally infested monkeys whose mesenteries had been exposed under anesthesia. The paired worms travel against the blood stream to the furthestmost possible point, where the female leaves her partner, and being of a smaller diameter, is able by means of her suckers to progress until she stretches the smaller venules to their uttermost. The ova are now deposited with their spines directed posteriorly in front of the anterior suckers. The female then withdraws a little and repeats the process. On the resumption of the blood current the vessel wall contracts upon the contained ova and drives the spine through the vessel wall. It would appear that ova, but freshly deposited in this manner in the submucosa of the bladder, are voided in the urine only a few hours subsequently, and it is due to the rupture of these small blood vessels that the blood leaks out into the urine at the same time."

S. hematobium, the species which causes urinary schistosomiasis, has been found to develop in the following fresh-water snails: *Bullinus contortus*, *B. dybowskii*, *B. innesi* and *B. africanus*. *S. mansoni*, the cause of intestinal schistosomiasis, finds its Egyptian host of preference in *Planorbis boissyi*, its Brazilian, in *P. olivaceus*, and in Venezuela, it seems to be satisfied with either *P. cultratus* or *P. guadalupensis*. *S. japonicum*, the cause of hepatic schistosomiasis is, according to Japanese authorities, the guest of certain species of *blanfordia*.

In the liver of the snail the miracidium becomes a smooth walled sac or sporocyst with daughter sporocysts, which develop the larval forms (cercariae). As the name implies, the cercariae consist largely of tails, each organism having two tails, constituting a large part of the parasite. The cercariae leave the snail, swim freely in the water, and are able to infest man by traversing either the skin or the mucous membrane of the alimentary tract; in other words, man, and indeed other animals, may become infested with these parasites by either external or internal application of water containing them. In experiments with these parasites it is quite important that the investigator should refrain not only from drinking the water containing them, but from allowing such water to come into contact with his skin.

Prevention.—It will be seen from what has been said concerning the parasites that in infested countries one must neither drink the water, bathe in it, nor even allow it to come into contact with his body. Fishing and hunting in endemic areas are accompanied by the possibility of acquiring the infection. The disease might be eradicated by efficient provision for the disposition of all fecal matter. Since even those who are not known to be ill and, at the time at least, have no sign or symptom, may be infested, the discharges, both urinary and fecal, of all must be treated and rendered harmless or discharged where there would be no possibility of infesting man. It should be understood that it is only the fresh-water snail which acts as a host for this parasite and there is no danger even when the water is slightly brackish. The individual can find protection in drinking only boiled water, in refraining

from bathing in suspected water and in keeping his feet dry when he walks abroad. It has been suggested by Leiper that schistosomiasis may be eradicated by the destruction of its snail hosts. With this in view, he suggests the periodic drying of Egyptian canals and the use of destructive chemicals. It is said that the cercariae can successfully traverse the ordinary municipal sand-filter bed and that within five hours they can penetrate 30 inches of fine sand.

Elgood and Cherry are quite sure that large rivers and rapidly flowing streams do not abound in snails which act as intermediary hosts for these worms. They hold that there is but little danger of infection from drinking unfiltered Nile water or from bathing in that river and claim that the most dangerous places, so far as this infection is concerned, lie in the numerous canals in Egypt. They state that the cercaria does not multiply after it has been discharged from the snail into water and that such immense volumes of water as the Nile carries can never become charged with these parasites to a dangerous degree. Men who have contracted the disease nearly always ascribe their infection to bathing in a small canal or in a pool filled from the canal, while among nearly 1,000 men who bathed freely in the river during 1916 no case of the disease has been reported. Snails are not easily seen on the banks of the Nile nor on the large or middle-sized canals, but on the smaller channels which ramify through every irrigated field. The percentage of fluke infestation among native children in Egypt under seven years of age is small, but at the age of sixteen it reaches twenty-five. Snails are abundant in the irrigation canals, whatever the source of the water with which they are supplied. On certain festival days, especially on the Coptic Easter Monday, Moslem and Christian take their children out for a good time, and this consists largely in allowing those who have reached the age of six or seven to wade in the small canals and ditches and to remain in them for a considerable time. These observers recommend the introduction into Egypt of large numbers of domestic ducks which, in their opinion, would aid greatly in ridding the country of the fresh-water snails whose existence is essential to the life of the parasite. They state that all but one of the ponds in the Zoological Gardens at Cairo are frequented by ducks, both tame and wild, and that the only pond in these gardens in which snails can be easily found is that filled with lilies and from which ducks are excluded. The keeping of ducks would not be an innovation, but an extension of native custom in widely distant districts. Besides, the birds might become a source of substantial profit to the inhabitants and a bonus could be offered for the production of unusual individuals. The same writers call attention to the fact that of two islands in the eastern Mediterranean—Crete and Cy-

prus—both in close communication with Egypt, Crete is free from the disease, whereas Cyprus is badly infected. In the former island, the streams have their origin in the mountains and flow rapidly all through the summer, whereas in Cyprus there are marshes and river holes in the summer—splendid places for fresh-water snails—offering certain enticement as baths for children. In some countries, even those where there is an annual heavy rainfall, streams are largely dry during the summer and their beds occupied by detached pools in which and about which snails abound. Such conditions are present in Venezuela, in some of the West Indian Islands, and in Mesopotamia, all of which are infected.

Manson-Bahr and Fairley say that the presence of species of fresh-water snails known to play a part in the life-cycle of this parasite in water should in and of itself condemn the water for drinking purposes, and they find that the treatment of such water with chlorin up to four parts per million does not destroy the cercariae. These investigators also urge that hunters are not safe in wading in infested waters at any time of the year. They recommend that fishers should wear rubber boots extending above the middle and that too much trust should not be placed in these as they may be penetrated by the cercariae. It seems that mounted troops in Egypt have become infested by riding their horses into the water. Orderlies supplying horse troughs have been infested.

II. Clonorchiasis

Description.—This is an infestation with a parasite, *Clonorchis sinensis*, independently discovered by McConnell in India and by MacGregor in Mauritius in 1874. It is widely scattered over oriental countries, including Korea, Japan, Formosa, China, and India. According to Katsurada, there are local areas in central Japan in which from fifty to sixty-five per cent of the population are affected. The parasite is most frequently found in certain domestic animals, notably cats and dogs, but its behavior in these in no way differs from that which it manifests in man. Its natural habitat is the gall bladder and its ducts. It distributes itself to the remotest parts of the liver where it may form abscesses and otherwise destroy the hepatic tissue. As a result of this irritation, the liver is enlarged, in which it may be accompanied by increased growth of the spleen. At first it was supposed that this parasite is harmless, but prolonged observation has demonstrated that infested individuals develop chronic diarrhea, accompanied by a gradually developing cachexia with anasarca and a general condition resembling that seen in sheep rot. It is a slowly progressing, but in the end a surely fatal, disease.

The Parasite.—The adult *sinensis* measures from 10 to 20 mm. in

length and from 2 to 5 mm. in breadth. It is eliminated from the intestines of infested men and animals. The ova find their way into some mollusk, and then seek for their second intermediary host some fresh-water fish, especially those of the carp family.

Prevention.—Avoid unnecessary familiarity with cats and dogs; drink only boiled water; eat only well-cooked food. The possibility of the contamination of vegetables which are eaten raw should always be borne in mind; especially is this of importance in countries where fresh fecal matter is largely used for the enrichment of garden soil.

III. Paragonimiasis

ENDEMIC HEMOPTYSIS

Description.—In 1878 Kerbert, in making autopsies on two Bengal tigers dying in zoological gardens, one at Amsterdam, the other at Hamburg, found in their lungs a hitherto undescribed parasite. He named this parasite *Paragonimus westermani*. One year later, Ringer found a similar parasite in the lungs of a patient in northern Formosa, and this was described and named *Distomum ringeri* by Cobbold in 1880. There has been and continues to be some discussion as to whether the human and the animal parasites constitute one or two species, with the weight of opinion at present in favor of two. Be this as it may, the family name suggested by Kerbert has the claim of priority and is now used to designate the disease. In 1880 Baelz and Manson, independently, found the ova of this parasite in the sputum of certain cases of chronic hemoptysis. These cases were seen in Chinamen in Formosa. In 1883 Baelz found the adult parasite in the lung and called it *Distomum pulmonale*. In 1890 Otani and Yamagiwa demonstrated that this parasite did not confine its depredations to the lungs, but could cause a general infection. In 1902 Musgrave described the disease as seen in the Philippines. Since that time it has been shown by Japanese physicians that this parasite is to be found in a considerable proportion of the inhabitants of northern Formosa. In 1913-1914 Nakagawa found in this region 1,249 cases, and estimates the number at not less than 13,000. It is reported to be most abundant among the half-savage tribes of the lowlands and to grow less frequent as one advances into the highlands. At present, paragonimiasis is known to occur in Japan, Korea, China, Formosa, and the Philippine Islands. It is possible, and indeed highly probable, that as world travel increases and peoples from the most remote corners come out and mingle with mankind at large, other countries will show evidence of invasion by this organism. The early students of this disease believed it to be confined to a peculiar pulmonary condition manifested by a chronic cough and the raising of blood-stained rusty sputum. In most

instances the hemoptysis is trifling, but in exceptional cases it is abundant, leads to marked anemia, and may threaten life. In these cases, examination of the sputum under a low power microscope reveals eggs from 80 to 100 microns in length and from 40 to 60 microns in breadth. It was found that if such sputum be allowed to stand for a month or six weeks, during which time it is frequently shaken with fresh water, the eggs will discharge ciliated miracidia.

On examination of the lungs of these cases at autopsy it will be found that scattered through the tissue there are excavations, some of which may be as large as a hazelnut, with communicating tunnels. These discharge into a bronchus and supply the ova found in the sputum. Occasionally there is found in these excavations or in the communicating tunnels, one or more of the adult trematodes. It is now known that any part of the body may be invaded by this organism; indeed, its distribution is sometimes quite general, leading to muscular pains, enlarged glands, and cutaneous ulcerations. The intestinal walls may be invaded and a diarrhea, with the eggs in the stools, may result. The invasion of the cord may be followed by neuritis or paralytic symptoms, and the presence of the trematode in the brain may induce Jacksonian epilepsy. Musgrave, who has added greatly to our knowledge of this disease, and especially to its pathology, states that the lesions may occur in the bronchial or intestinal mucosa, in the bile duct or in the skin, and that they may be tubercular, suppurating, nonsuppurating or ulcerative. This investigator reports the finding of not less than 100 mature parasites in a psoas abscess.

The Parasite.—*P. westermani* in its adult form measures from 8 to 20 mm. in length and from 5 to 10 mm. in breadth. It has both an oral and a ventral sucker. The habitat of the adult is the tissue of man and other animals. As we have seen, the eggs are coughed up and may be eliminated with the feces. So far as we know, they have not been found in the urine. After elimination from the animal body, the eggs find their way into water where they are hatched, producing free-swimming miracidia. These take up their residence in an intermediary host, which is some species of fresh-water snail. In the liver of this animal they become sporocysts, with daughter sporocysts, and eventually escape into the water as free-swimming cercariae. These seek another host, which is generally a fresh-water crab, and take up their residence in the liver or muscles where they multiply. They may find their way into man or other animals in the food or drink. When experimentally introduced into cats they apparently hasten to the lungs and hemoptysis may follow within ten days.

Prevention.—The excretions of infected persons or animals must not

be permitted to find their way into drinking water. It will be best and safest not to drink unboiled water. It is certainly wise not to eat uncooked snail, crab, or fish in infested localities. In Japan invasion is generally attributed to the eating of raw fish, but it is claimed that in neither Korea nor Formosa are crabs, snails, or fish eaten uncooked, and still in these countries the disease is more prevalent than it is in Japan. It is an undecided question whether encystment in a second fresh-water animal is a biologic necessity in the life-cycle of this parasite.

IV. Classification and Distribution of Trematodes

With considerable modification of the tables of Kanter, we are presenting the following condensed statements concerning the classification and distribution of the known trematodes:

Fasciola hepatica.—A parasite of herbivorous animals; causes rot in sheep; between 30 and 40 cases of human infection have been reported in Europe; according to Saito, 16 $\frac{2}{3}$ per cent of the cattle in the Province of Okayama, Japan, carry this parasite; it is transferred to man by the eating of raw vegetables and by the drinking of contaminated water; according to Schilling, human infection is not rare in Tonkin, and Day and Jeffers bear similar testimony from observations in middle China; it is said that in the region of Lebanon in Syria the natives eat raw liver carrying this parasite, which attaches itself to the walls of the pharynx causing a disease known as "halzoun."

Fasciola gigantica.—A giant form of the preceding; a parasite of herbivorous animals in tropical Africa and Asia; one case seen in Rio de Janeiro, probably imported from Senegambia.

Fascio'opsis buski.—Common in pigs; seen in a lascar at the Seamen's Hospital in Greenwich; found in a man by Kerr in Canton, China; apparently rather widely disseminated in man in China, Siam, and Dutch East India; one case seen in Germany and one in Galveston, Tex., both imported.

Fasciolopsis füllebornii.—Seen at Hamburg in a man from Calcutta.

Fasciolopsis rathouisi.—Found in man in China.

Fasciolopsis goddardi.—Imperfectly known; found in man in China.

Echinostoma ilocanum.—Found by Garrison five times in the examination of 5,000 stools in Bilibid Prison in Manila; five more cases in the Philippines have been reported by Hilario and Wharton; found in man in China.

Echinostoma malayanum.—A parasite of dogs and cats; reported among men in the Malay States, north Siam, and Assam.

Dicrocoelium lanceatum.—A parasite of herbivorous and omnivorous animals; widely distributed over Europe, Asia, Africa, North and South

America; found in man, though rarely, in North America, France, Switzerland, Germany, Bohemia, and Egypt.

Heterophyes heterophyes.—A small hermaphroditic trematode; a parasite of dogs and cats; found during the World War on the Sinai Peninsula 33 times among 1,673 Egyptian workers and twice among 2,082 Europeans; the white men had been in Egypt only a short time; Acton reported one case in Mesopotamia; this, however, was in an Indian who may have carried the infection with him from his native country; this parasite has not been found among men in eastern Asia.

Metagonimus yokogawai.—Discovered by Yokogawa in 1913 in northern Formosa; its first intermediate host is a snail; its second intermediate host is a fish of the trout family; it is customary among the natives of Formosa and adjacent countries to cut these trout in strips, dry them, and eat them raw; in northern Formosa whole villages are infected by this fluke; an examination of 458 Japanese students showed this parasite present in six per cent; an examination of 326 Koreans disclosed the parasite in only two; it is suggested by Kanter that the parasite has been carried to Korea by the Japanese.

Paragonimus westermani.—Previously discussed; found in cats and dogs in Michigan, Wisconsin, and Ohio; found in man in Japan, Formosa, Korea, Philippine Islands, Indo China, Sumatra, Yucatan, and Peru; discovered in Germany in two Americans, one coming from California, the other from Missouri (doubtful).

Opisthorchis felineus.—A parasite of cats, dogs, foxes; found in Asia, Europe, and North America; a case reported by Ward in Nebraska; found in man in Prussia, Russia, Siberia, middle China, and Siam; according to Winogradoff, it is the most widely distributed human parasite in man in Siberia; in eastern Asia and in middle China it is reported that man and cats frequently bear this parasite; its cercariae are found in a small fish which in China is usually eaten but partly cooked; it has not been found in man in the United States.

Opisthorchis neverca.—First seen in the liver of dogs in Calcutta by Lewis and Cunningham in 1874; in Japan this fluke is found in cats; a case was reported by Musgrave in a Chinaman in the Philippines.

Clonorchis sinensis.—Previously discussed; found in man in Formosa; Korea, Japan, China, Siam, Dutch East Indies, and the Philippines; Kanter states that the western coast of the United States is in danger of wide infestation with this parasite and that twenty per cent of the Chinese immigrants to this country bear the parasite; imported cases from China and Japan are found in California.

Clonorchis endemicus.—Reported by Okayama in Japan; seen in Tonkin and Annam.

Metorchis truncatus.—A parasite of domestic animals—sheep, cats,

and dogs; only one case seen by Winogradoff in man; this was at Tomsk, Siberia.

Schistosomum hematobium.—Previously described; widely prevalent among men in Africa, especially in Egypt, in southern Asia, and in the Dutch Indies; only imported cases seen in Europe and the United States.

Schistosomum mansoni.—Seen rarely among men in the southern United States; more frequently in Central and South America and the West Indies; found quite widely distributed over Africa.

Schistosomum japonicum.—Previously discussed; found among men in Formosa, Japan, Korea, China, and the Philippine Islands; cases imported from the Philippines seen in the United States, and from Egypt, Salonika and Malta, in England.

Gastrodiscus hominis.—A parasite of herbivorous mammals; first found at autopsy in man in 1857, and rarely seen in India since that time; one case reported in a soldier in the Philippines by Tuttle.

Cladorchis watsoni.—But little known; reported as a parasite of ruminating animals at Adamawa, a country in West Africa, lying roughly between 6° and 11° north and 11° and 15° east, about midway between the Bight of Biafra and Lake Chad; only one case of human infestation known; this was in a negro from Adamawa who was suffering from a diarrhea; the parasite was found in the stools during life and in the small intestine after death.

Bibliography

- CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, 1919.
CAWSTON, F. G.: Parasitology, 1917, iii, 131.
ELGOOD, MRS. B., AND CHERRY, T.: Lancet, October 11, 1919.
HERZOG, H.: Philippine Jour. Sc., 1908, ii, 1.
KANTER, H.: Janus, 1921, xxv, 129. (Complete list of recent literature.)
KOBAYASHI, H.: Parasitology, 1920, xii, 380.
LEIPER, G.: Jour. Roy. Army Med. Corps, 1915, xxx.
LINTON, E.: Biological Bulletin, 1915, xxviii, 198.
MADDEN, C.: Bilharziosis, London, 1907.
MANSON-BAHR, P., AND FAIRLEY, N.: Parasitology, 1920, xii, 33.
MANSON-BAHR, P.: Manson's Tropical Diseases, Seventh Edition, 1921.
WARD, H. B.: Jour. Parasitology, 1916, iii, 10.
YOSHIDA, S.: Jour. Parasitology, 1916, iii, 76.

CHAPTER XVII

SOME CESTODE INFESTATIONS

General Statements.—It is a reasonable presumption that Moses knew something about tapeworms when he forbade the children of Israel to eat pork. At least, it is evident that tapeworm infestation was known in ancient times in Egypt and adjacent countries, and the proscription of pork as an article of diet was extended to his followers by Mohammed. Greek physicians were quite familiar with tapeworms, which they describe with sufficient accuracy to show that they knew the parasites which we are now discussing. About the close of the sixteenth century physicians recognized two forms of tapeworm, *taenia* and *bothriocephalus*. In 1683 Tyson described the head of a tapeworm which he had found in a dog, and about the same time Redi came to the conclusion that *cysticerci* are animals. In 1851 Küchenmeister demonstrated by feeding experiments that *cysticerci* are larval forms of tapeworm.

The cestodes which infest man are segmented worms, varying greatly in length from a fraction to several meters. In most of them the adult animal has its habitat in the alimentary canal of man and its larval life is passed in some other animal. In rare instances, such as the *echinococcus*, the adult lives in some animal and the encysted stage is passed in man. Still more rarely, as may occur with *T. solium*, man may harbor both the adult and the encysted forms. The adult tapeworm has a head, technically known as the scolex, furnished with multiple suckers by means of which the animal attaches itself to the walls of the intestinal canal. In some species, in front of these suckers is a projection known as the rostellum, which may or may not be armed with hooks, varying in number according to the species. The apparent purpose of these hooks is to aid the suckers in enabling the animal to attach itself to the intestinal wall. Behind or below the head is a narrowing of the body known as the neck and beyond this lie the segments known as proglottides, which are widely variable in number and in size with the species. There is no alimentary canal and the parasite receives its food from the intestine of its host by osmosis. There is, however, an excretory system, which consists of anastomizing tubules emptying on the surface. There is a rudimentary nervous system consisting of one ganglion in the scolex with two cords which pass through the segments and are provided with branches.

The outer layer of the worm consists of cuticle containing a large

quantity of lime. Moreover, there are calcareous corpuscles found widely distributed throughout the parenchyma. The large amount of calcareous material perhaps serves a double purpose, that of supplying a skeletal support and that of furnishing material for the egg shells. The muscular system consists of both longitudinal and transverse groups. As each segment, or proglottide, matures it develops sexually and is provided with both testes and ovaries. One segment may impregnate its own ova and may pass any excess of seminal fluid to a neighboring segment. There are multiple testes, which are connected with one another by tubules, and their secretions pass finally into the vagina where they await the coming of the eggs. There is a lobulated ovary, in some species two or more, which discharges its products into a common oviduct, emptying into the uterus and thus coming into contact with the male elements. The ova, having been impregnated, are supplied with yolk material and surrounded by shells. The uterus is packed with impregnated ova and the development of the egg content begins in the uterus. When a segment has become sexually mature and carries its complement of fertilized eggs, it drops its connection with the segment lying in front of it and is discharged from the alimentary canal of the host.

The expelled segment undergoes disintegration in the outer world and the impregnated forms must find admission to the alimentary canal of a new host or soon perish. When taken into the stomach of the new host the embryos are set entirely free by the action of the gastric juice and, piercing the walls of the small intestine, seek some place where they may encyst themselves in the tissue. The cysticercus, or encysted larva, sets up an inflammatory reaction, which leads to its enclosure by the formation of a cyst wall at the expense of its host. In this, which is known as the cysticercus condition, the parasite remains until the flesh in which it is encysted is eaten by some other animal, and in the intestine of this host the parasite again reaches its adult stage. As a rule, the cysticercus has its natural habitat in some herbivorous animal, while the adult develops in some carnivorous or omnivorous animal. If the cysticercus is not within a time, which varies with different parasites, transferred to a second host, it ultimately undergoes calcareous degeneration.

Taenia solium.—This worm usually measures from two to three meters, though it may be two or three times this length. It carries a globular head with a short slightly pigmented rostrum bearing from 25 to 50 hooklets. There are four circular, slightly projecting suckers of about $\frac{1}{2}$ mm. in diameter. The proglottides gradually increase in size from the head downward until they reach maturity with a length of about 12 mm. and a breadth of about 6 mm. Usually from four to six sexually ma-

ture segments are passed at a time with the stools. These segments undergo a natural disintegration or they may be swallowed still intact by their second host. In case of *Taenia solium* the second host is a hog. In this animal the ciliated embryos pass through the intestinal walls and become cysticerci. Hog flesh infested with these cysticerci has long been known as "measly pork." In the gastric juice of man the parasites are set free and the liberated scolex enters the small intestine, attaches itself by its suckers and hooklets to the wall and begins anew the formation of segments.

It seems desirable to point out here that the word "solium" does not mean alone, and it is not right to infer from the name that this worm always occurs singly in man's intestine. Two or more may be found at the same time in the same individual. "Solium" apparently was attached to the name of this worm by the Arabs some centuries ago and it means a chain and refers to the segmented character of the parasite.

A healthy man may carry an adult *Taenia solium* quite indefinitely without any marked disturbance in health, but there is no reason why even a healthy man should support such a parasite. In children and in debilitated adults *Taenia solium* is often a factor having more or less to do with the inability of its host to regain or retain a fair degree of health. It is possible, though it rarely happens, for a man carrying the adult to become also the host of the cysticercus form. This is especially true should he swallow the eggs which have come from his own body; in other words, repeated autoinfection may occur among those who carry this parasite, and the damage done by the encysted form depends upon its location. In the eye or in the brain it may be quite a serious matter.

Infestation with this worm is likely to occur wherever man eats pork, and especially when he eats it without thorough cooking. The geographical distribution of this infestation is coextensive with that of man and the hog whenever the former feeds upon the latter. Orthodox Jews and Mohammedans, as well as strict vegetarians of other religions, are never infested with *Taenia solium*. Among those who do eat pork the frequency of this infestation depends upon (1) the chances afforded hogs of eating human feces or food contaminated with such feces; (2) inspection of pork at the slaughterhouse and the exclusion of infested meat from the markets; (3) degree of heat to which pork preparations are submitted before they are eaten. It is quite plain that taenia infestation is more likely to occur among primitive people whose feces are scattered freely about their habitations and over the ground traversed by their pigs. The frequency with which taenia infestation

occurred in American pork led to the establishment of federal inspection of all meats sent abroad. Meat preserved by smoking or by the application of common salt or nitrate of potash is not safe eating without thorough cooking. Quite naturally, people who are accustomed to eating partially cooked pork are most likely to be infested.

Taenia saginata vel mediocanellata.—This tapeworm, which usually measures from five to ten meters and may be longer, passes its cysticercus stage in cattle and its adult life in the intestines of man. It has four hemispherical pigmented suckers and is without rostellum or hooks. In place of the rostellum there is a fifth sucker. The sexually mature segments pass with the feces to the external world and, disintegrating, permit their contained embryos to spread through the grass where they are swallowed by cattle. In the ox this parasite passes its cysticercus life and awaits the time man swallows the beefsteak containing it.

The frequency with which this infestation occurs depends upon the extent to which the pasturage of cattle is contaminated by the excretions of infested men and upon the thoroughness with which beef products are cooked before they are eaten. In India, Mohammedans and Europeans are frequently infested with this parasite, while this rarely occurs among the vegetarian Hindoos.

Statistics of the Bureau of Animal Industry show that nearly one per cent of all cattle slaughtered in the United States carries this cestode infestation. The ox becomes infested by eating food or drinking water contaminated with the feces of an infested man, and man becomes infested by eating the raw or partly cooked flesh of infested cattle. Comparing the two tapeworms, Ransom says:

“The pork tapeworm is a more dangerous parasite than the beef tapeworm on account of the fact that the intermediate stage may develop in man if the eggs are swallowed, and as the cysts may lodge in vital organs, such as the brain or heart, the consequences are liable to be serious. Fortunately the pork tapeworm and its intermediate stage are very rare in the United States, and this is explained by the fact that in this country raw or imperfectly cooked pork is rarely eaten. Thorough cooking invariably destroys the vitality of tapeworm cysts, and consequently in this country there is little chance that tapeworm cysts in pork will reach a human host alive. Inasmuch as the limited use of raw or imperfectly cooked pork insures the rarity of the pork tapeworm in man, it naturally follows that the intermediate stage in hogs will also be rare, because hogs become infested with the cysts only as a result of swallowing the eggs which occur in the feces of human beings infested with the pork tapeworm. The beef tapeworm and its cystic stage, unlike the pork tapeworm, are comparatively common in the United States, the explanation being that raw or rare beef is very frequently eaten. Beef measles at the present time is thus of much greater importance in the United States than pork measles. Although less dangerous than the latter, it is more or less harmful to health, and consequently as a public health measure the meat of cattle infested with measles must either be excluded from the market, or, in

cases of slight infestation, after removal of the few cysts found, must be so treated by refrigerating, cooking, or pickling as to render harmless any parasites which may have been overlooked by the meat inspector.”

The cysticerci of beef tapeworm are distributed about equally between the muscles of the head and the heart. Compared with these muscles the parasite is found about one-third as often in the diaphragm and about one-fifth as often in the tongue. In inspecting slaughtered animals for this parasite special attention is given to the muscles of the head and heart. If the carcass is heavily infested, showing a wide distribution of cysticerci throughout the muscular system or, without reference to the number of parasites, if the flesh is watery or discolored as a result of the parasitic invasion, it is condemned. Slightly infested carcasses may be passed for food after three weeks' refrigeration or pickling, or after being cooked. If all infested meat could be excluded from human consumption this parasite would become extinct, but there is no practical method of meat inspection which would absolutely insure the freedom of all meats from cysticerci. In order to reduce to a minimum the chances of this infestation, beef and pork should not be eaten unless thoroughly cooked. Even with this precaution, there is the possibility of an occasional infestation, as, for instance, when a careless cook uses the same knife, first in cutting the raw infested meat and, second on cooked meat or even on bread or some other food.

Dibothriocephalus latus.—This is known as the broad tapeworm and on account of its shape was distinguished from taenia quite 300 years ago; while the distinction between *Taenia solium* and *Taenia saginata* was not made until about the middle of the nineteenth century. The broad tapeworm has a wide distribution throughout the world, but it has long been observed that it is most frequently seen among those who live in coastal regions and who eat fish, especially fresh-water fish. Hirsch in 1886 wrote concerning the distribution of this parasite, as follows:

“A glance at the distribution area of *bothriocephalus* will show us that it is mostly *indigenous to the sea coast and to the shores of lakes and other inland waters*. The Swedish practitioners are clear in their statements that it is almost exclusively the inhabitants of the coast who suffer from it, those dwelling even a few miles inland being nearly exempt. Zaeslein, also, has shown with much exactness that the same holds good for Switzerland. In that country he distinguishes four zones of frequency. The first of these, embracing the villages lying close down to the lakes, is to be regarded as the proper area of infection. In the second, comprising the country one to four leagues inland from the lakes, the parasite is much rarer; it no longer occurs, as in the first zone, among all classes equally, but more frequently among the industrial part of the population, and less so among the agricultural, the inhabitants of that zone becoming infected for the most part not at home but during their visits to the lake shore. As regards the third zone, comprising the towns, large and small, at a distance of more than five leagues from a lake, the infection may in most cases be traced with

certainly, or at least with probability, to the French Alpine departments, although there are a few places, such as Burgdorf and Thun for which the autochthonous occurrence of the parasite cannot be altogether denied. Finally, in the fourth zone, distant from the lakes, more than six leagues, bothriocephalus is met with either in mere occasional cases, or not at all.”

This is a grayish worm which may measure as much as ten meters. Multiple worms in the same individual are not infrequent. The scolex is oblong and is not provided with suckers, rostellum, or hooklets. Extending throughout the length of the parasite are two grooves called bothria or long suckers. The number of segments in a single parasite may reach three or four thousand. The adult of this parasite has its habitat in the small intestine of man, dog, or cat. The embryos, carried from these hosts into the outer world by the discharge of impregnated segments, find their way into the water, and in this element they pass successively through two intermediate hosts. First they penetrate and pass through a part of their life-cycle in certain fresh-water crustacea, such as *Cyclops strenuus* or *Diaptomus gracilis*. In the intestinal canal of these crustacea they are transformed into hairy larvae. From the crustacea these larvae pass into the stomachs of fish, especially trout, perch, and pike. They penetrate the intestinal walls of these—their second hosts, and become encysted in the flesh of the fish. When man, dog, or cat eats the fish the cell walls enclosing the larvae are digested and the young develop into adults in the intestines.

A second species of this genus, known as *Dibothriocephalus mansoni*, was first found by Manson in 1882 in making an autopsy on a Chinaman in Amoy. Manson found these parasites lying under the peritoneum near the kidneys and free in the pleural cavity. They looked like strings of fat until taken out, when they showed feeble but distinct movements. According to Manson-Bahr, 55 cases of this parasite in man had been detected up to 1921. The normal habitat of the adult of this species is the intestinal canal of the dog or cat. When the ova are discharged they find their way into the water and enter a crustacean, *Cyclops leuckartii*. After a stage of development in the *Cyclops* the larvae are ingested by a frog, *Rana nigromaculata*, or a snake, *Elaphe climacophora*. In the adult they reach a length of from 8 to 40 cm. This worm is flat, unsegmented and carries on the ventral surface a longitudinal median groove, while on the dorsal surface there may be two grooves. This species is sometimes eliminated through the urinary bladder and may block the urethra in seeking its exit to the outer world.

Taenia echinococcus.—In the case of this parasite the host of the adult is a dog, wolf, or some other member of the canine family. In these animals this parasite, which is one of the smallest tapeworms known, measuring in length only from 2.5 to 6.0 mm., lies between the villi of

the small intestine. Its segments, which number usually more than four, reach sexual maturity only in the last. When these are discharged in the feces of the dog and become mixed with human food and are taken into man's stomach, the cysts are digested and the embryos pass through the intestinal walls and establish themselves in cysts somewhere in man's body; most frequently in the liver; less frequently in the lungs or kidney, and still less frequently in the brain. The cysts formed by these parasites are surrounded by a wall, provided at the expense of the tissue of the host, consisting of two layers, an ectocyst and an endocyst. These hydatid cysts produce the symptoms of tumors and may become of considerable size—several inches in diameter. These cysts develop smaller ones known as daughter cysts and granddaughter cysts, and these may develop either inside or outside of the mother cyst. The cysts are filled with a fluid in which the larval scolices float. Manson-Bahr makes the following statement concerning this infestation:

“Man becomes infested by too close association with the usual definitive host, the sheep dog. The ova are ingested by using the same dishes as these animals, by kissing infested dogs, and it is also possible that house-flies may disseminate the eggs from the feces of these animals. Persons of all ages are liable to infestation, but the disease known as hydatids is more common in children under ten years. The symptoms to which hydatids may give rise are very varied, according to the site of the cyst. They may include symptoms of toxemia, such as pyrexia, urticaria, and multiform cutaneous eruptions. On the other hand, the fully developed cyst may appear as a tumor, especially on the liver, and this, on bursting, forms secondary cysts in other organs, or may suppurate and cause general peritonitis. In the brain hydatids give rise to symptoms of cerebral tumor; while those of the liver, spleen, and peritoneum are liable to stimulate malignant growths. Hydatids of the lung give rise to symptoms of compression with the formation of fluid in the pleural cavity. The kidney may be converted into a mass resembling hydronephrosis.”

Hydatid cysts are most frequently found among people who live intimately with dogs. They were formerly highly prevalent in Iceland. In 1886 Hirsch wrote:

“The Iceland cowherds have notoriously little sense of cleanliness, and they are all the more ready to share with their highly treasured dogs not only their dwellings but their platters also, and even their beds, because the risk of infection from the dog is a thing unknown to them. Furthermore, the dogs have free access to the storerooms, whose contents they befoul with their dejecta; and it can only be because a few out of the many thousands of taenia eggs entering the human intestine ever reach the mature stage of bladder-worms, that a very much larger number of persons in that country do not suffer from echinococcus. Finsen is explicit in stating that the parasite is hardly met with among the more civilized of the Icelandic population, among families occupying commodious houses and duly practicing cleanliness.”

At one time hydatid disease was widely prevalent among the pastoral population of Australia. In this connection it may be well to say that sheep, as well as man, may carry the cysts. The shepherd

dogs carry the adults and distribute the embryos over the pasturage upon which the sheep feed, and in this way a vicious circle, involving the dog, the sheep, and occasionally man, is established.

While hydatid cyst is not frequent among the more intelligent classes of Europe and America, it is not wholly unknown among these. The ova from dogs may be deposited upon growing vegetables and when these are eaten without being cooked, infestation may and does occasionally occur.

Taenia nana.—This is the smallest tapeworm which has ever been found in man. The adult measures only from 5 to 50 mm., but the number of segments may run as high as 200. It has not been definitely shown that this parasite has an intermediate host. It seems that both the adult and the cysticercus stage may be passed in the intestinal canal of the one animal. It is quite certain, however, that the cysticerci cannot develop until they have been acted upon by a gastric juice. Grassi has experimentally studied the development of this parasite in the rat. Eggs swallowed by this animal after passing through the stomach are hatched in the small intestine and there transformed into cysticercoids which are provided with tail-like appendages and are, consequently, known as cercocysts. These cysts never develop into adults until they are conveyed to the same host or some other animal by the mouth; in other words, the egg will not hatch until it has been subjected to the action of the gastric juice. Grassi fed eight persons with sexually mature segments of the parasite from both man and rats; only one of these became infested, but this occurred in a region where this tapeworm is common and it is not certain that the infestation originated in the feeding. From an epidemiologic standpoint it is well to consider infestation with this cestode as a communicable disease which may be transmitted from one person to another. This form of parasitic infestation is probably quite widely distributed over the earth. It was first detected by Bilharz in the small intestine of a boy who died in Cairo of meningitis in 1852. Calandruccio estimates that ten per cent of the children in Sicily carry this worm, and Stiles found it in 4.8 per cent of 125 children examined in Washington. Children carrying this parasite should be isolated until relieved of it; their feces should be safely disposed of even if individual disinfection is necessary, and they should be instructed to carefully disinfect their hands after going to stool. Fortunately, this, like many other species of intestinal tapeworm, may be expelled from the intestine by the proper administration of the extract of male fern. If we regard the rat as a distributing agent for this parasite, we have only added another to the many reasons that we have for exterminating this pest.

Taenia leptocephala.—This is also known as *Hymenolepis diminuta*

and is a small tapeworm found in the rat. It has been seen in man only in a few instances in the West Indies, South America, Italy, and the Congo. It is believed that the cysticercus stage is passed in some insect; in rat-fleas and in certain coleoptera. It is claimed that the rat becomes infested by eating its own fleas, and accidental infestation may occur in man by eating insufficiently cooked bread after beetles have had access to the flour.

Taenia canium.—This is a common tapeworm found in cats and dogs in central and southern Europe. It has been found, though rarely, in children in Spain, Italy, and southern Germany. The cysticercus stage is passed in fleas and lice.

Taenia africana, **T. hominis**, **T. philippina**, and **T. asiatica**, are probably varieties of *T. saginata*. The same thing is possibly true of **T. confusa**, a name proposed by Ward for a tapeworm $8\frac{1}{2}$ meters long, seen and described by him at Lincoln, Nebr., in 1896.

Bibliography

- CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, 1919.
HIRSCH, A.: Handbook of Geographical and Historical Pathology, 1886, ii.
LEUCKART: Parasites of Man, 1886.
LOOSS: Mense's Handbook of Tropical Diseases, 1905.
MANSON-BAHR, P.: Manson's Tropical Diseases, 1921.
MEGGITT, F. J.: Parasitology, 1920, xii, 301, 310.
RANSOM, B. H.: Bureau of Animal Industry, 1911, Circular 214.

CHAPTER XVIII

SOME NEMATODE INFESTATIONS

General Statements.—The order of nematodes comprises many genera and an undetermined number of species, most of which are parasitic at some period in the life-cycle. They are round nonsegmented worms, generally white, sometimes yellowish or pinkish, and consist of male and female. The mouth, guarded by two or more lips, opens into a suctorial esophagus, which terminates in a thin walled intestinal canal, opening by a chitinous rectum into an anus which is located near, but anterior to, the posterior extremity of the worm. The animal is covered by a thick cuticle, which, in some species, carries spines, fins or hooks. The epidermis consists of a muscular layer with inward projections which are connected with the nerves and the excretory tubules. The excretory organs are made up of two longitudinal canals connected anteriorly by a transverse bridge and opening posteriorly on the ventral surface.

The rudimentary nervous system consists of an annular gland about the esophagus, from which fibers branch throughout the length of the worm.

All species of this order furnish male and female, the former being smaller and shorter than the latter. The male organs of reproduction consist of convoluted tubules, which serve in their course as testes, vas deferens, and vesicula seminalis. Similarly in the female, the reproductive organs consist of coiled tubes, the anterior ends of which serve as ovaries, the middle as oviducts, and the terminal parts as uteri. The life-histories of the nematode parasites that infest man will be discussed in the descriptions of the individual species.

Ascaris lumbricoides.—The round worm, as it is popularly known, resembles in appearance, size and shape the earth-worm, though it is generally less red in color. This worm apparently is widely distributed over the world, epidemics of this infestation having been reported from Greenland southward through all the zones. The frequency of infestation with this parasite depends upon the habits of the people and it is rather difficult to believe the stories told by medical men of their observations in certain countries. Dyer, writing in 1834, makes the following statement:

“This complaint is nearly universal in Mauritius. * * * In the black population in such numbers are the lumbrics produced, that I have frequently been disgusted by seeing them crawling from the anus and mouth at the same time. One black literally brought me his hat full, which he assured me he had passed very shortly before.”

This is a round yellowish or brownish worm, spindle-shaped, with the female measuring from 25 to 30 cm. in length and the male about two-thirds this size. The mouth is surrounded by denticulated lips. At autopsy it is usually found, most abundantly at least, in the small intestine, though in rare instances, it may be seen anywhere in the alimentary canal from the esophagus to the rectum, and still more rarely, in the nose, larynx, trachea, and bronchi. Occasionally it causes abscesses in the liver, pancreatic duct, appendix, and in the muscular body walls. The eggs are from 50 to 75 microns in length and from 40 to 50 microns in breadth and are covered by an albuminous coat, usually stained with fecal matter. The eggs are deposited in the small intestine and are eliminated with the feces. In the external world the eggs bear, without destruction, marked alterations in moisture and temperature. They are not destroyed in the soil by desiccation and it is possible that in dust they may be scattered through the air and inhaled. More frequently, they are washed into water-supplies or are deposited upon fruits and vegetables. Where night soil is used as field or garden fertilizer the possibility of the ova finding their way into the alimentary canal of man is greatly enhanced. Stiles has shown that the house-fly may carry the eggs which pass through the body of the insect unaltered and still capable of producing young.

If there be an intermediate host for the ascaris it has never been discovered. It has been believed until recently that man swallows the eggs with his food or drink and that these, after passing through the stomach, develop into the adult forms in the intestine. Recent investigations by Stewart and others show that in the lower animals at least, larvae from the eggs deposited in the intestine penetrate the liver and lungs where they undergo development and then return to the alimentary canal. While strong adults may carry many of these worms in their intestines without marked recognizable injury to health, it is undoubtedly true that they reduce the efficiency of all and seriously interfere with the well being of children. Besides, there is always the possibility that they may cause abscesses in the intestinal walls, especially in the appendix and in the liver.

Prevention of this infestation is secured by the proper disposal of fecal matter. It must be remembered, however, that dogs and possibly hogs carry these worms and their excretions may contaminate the drinking water or food of man. Santonin has long been relied upon as a specific in this infestation.

Oxyuris vermicularis.—This parasite, vulgarly known as the pin or thread worm, measures in the female about 10 mm., while the male is

seldom more than one-half this length. The male carries a curved or spiral posterior extremity provided with a hook-like terminal.

The habitat of the adult worm is near the vermiform appendix. When the female is impregnated she moves to the lower part of the large intestine where she deposits her eggs and from which both the mother and the eggs may pass with the stools into the outer world. The eggs when leaving the body of the female contain embryos which have almost reached larval maturity. These worms cause a most distressing pruritus ani, which interferes with sleep and induces a nervous condition. Inspection through a speculum may show coiled masses of hundreds of these worms lying just within the sphincter ready for expulsion. They may penetrate the mucocutaneous covering in and about the anus and cause a most persistent itching. Recently, Kofoed and White found a closely related species, *Syphacea obvelata*, in 427 out of 140,000 American soldiers. This worm is about twice the length of *O. vermicularis*. No intermediate host has been found for this parasite and those who carry it no doubt frequently reinfest themselves and endanger others by scattering the worms in their excretions.

Trichuris trichiura, **Ascaris trichiura**, **Trichocephalus hominis**, and **T. dispar**.—Under these scientific names the parasite, ordinarily known as the whip-worm, is widely distributed both in temperate and tropical latitudes. It is a whitish or pinkish worm, measuring in the female from 45 to 50 mm. in length and in the male from 40 to 50 mm. The eggs are brown and measure 50 by 25 microns. The natural habitat is in the cecum and in certain tropical countries it is found in more than half the inhabitants. The eggs are eliminated in the feces unsegmented and it requires 12 months or longer, depending somewhat upon temperature and moisture, for the development of the embryo. It is claimed that owing to the thickness and strength of the shell, the unhatched embryos may bear without harm many adverse conditions and that they may retain their vitality for several years. Powell states that there is only one male for nearly 500 females. Fortunately, this parasite, even when present in great numbers, is without recognizable effect upon its host, though it is claimed by some that it may occasion intestinal disturbances and possibly may be an infrequent factor in the development of appendicitis.

Trichina spiralis.—So far as injury to health and danger to life are concerned, this is the most important nematode which infests man. Epidemics of what we now know as trichinosis have occurred in central Europe, especially in Germany, during the last two centuries. Definite history of the disease, however, does not extend back farther than 1828, when Peacock deposited in the museum of Guy's Hospital muscle prep-

arations containing calcified trichinae. Five years later Hilton wrote of "oval bodies, transparent in the middle and opaque at their end, altogether about one twenty-fifth of an inch in length" which he found in the respiratory muscles of a man. With the best microscope at his command Hilton could detect "no organization" in these bodies, but he believed them to be cysticeri. In 1835 Paget carried a piece of muscle containing incapsulated trichinae to Owen, who succeeded in making out the parasite, its position within the capsule, and its characters. Owen coined the name *Trichina spiralis* and is usually accredited with its discovery. It seems that at the same time that Owen was studying his specimens, Wood, of Bristol, was finding numerous trichinae in the muscles of a patient who died after entering the hospital under the diagnosis of acute rheumatism.

It was not until during the sixties of the nineteenth century that the trichina was recognized as a harmful and even a deadly parasite. About that time epidemics of trichinosis began to be reported from widely distant parts of Europe and from both North and South America. American pork came to be regarded as dangerous and it was stated at that time, probably on insufficient evidence, that four per cent. of all the swine in the western states were trichinous. European governments forbade the importation of American pork or, indeed, of any American meat not only on account of infestation with tapeworm, but also on account of the more serious infestation with trichinae. This led to the federal inspection of meats exported to foreign countries, and later for all meats sold outside of the state in which the slaughtering is done. The trichina is a white worm from 1 to 2 mm. in length and barely visible to the unaided eye. The female is about twice as long as the male and is viviparous. The adult dwells in the small intestine and the young migrate into muscles and there encyst themselves. In addition to man, the natural hosts of this parasite include hogs, both tame and wild, rats, and lizards. Infestation results from eating imperfectly cooked or raw flesh in which larval trichinae are encysted. Man gets his infestation altogether from pork and within two or three days after eating trichinous meat the adults may be found in the intestine. Male and female lose no time in copulation and the embryos travel through the tissues of the host, encysting themselves by preference in striated muscles, with apparent special fondness for the muscles of the diaphragm, the intercostal and laryngeal regions. In the encysted form the parasites may retain their vitality for months and even for years. Both the adult and larval forms may greatly disturb health and endanger the life of the host. The adults in the intestines cause much irritation, including symptoms of dysentery, with blood-stained mucous stools and with the

development of a temperature which may run to 106°. At the same time, the larval forms are making their journeys through the various tissues of the body, causing difficulty in respiration, in mastication, possibly in vision, more rarely interfering with brain function and manifesting their effects in delirium. When the embryos are numerous and are taking up their more permanent abodes in various tissues of the body, ill effects are evidenced by edema of the feet, legs, abdomen, and face, with a rapidly progressive anemia. These symptoms may be mistaken for food poisoning, dysentery, typhoid fever, and virulent forms of rheumatism. When several people in the same family or in the same neighborhood develop these symptoms about the same time, trichinosis should be suspected; the parasite should be sought in the stools and the removal of small pieces of deltoid in search for the encysted form may be justified. It is customary to group the symptoms of trichinosis as follows: (1) That of gastrointestinal irritation; (2) muscular pain; (3) emaciation and marked anemia.

The frequency of trichinosis depends upon the extent to which the hogs are infested and upon the habit of eating pork raw or imperfectly cooked. Trichinosis has been most in evidence in Germany and in this country among Germans, because of the habit of these people of eating raw or imperfectly cooked pork in one of the many kinds of sausage in the preparation of which they are so adept.

When the microscopic examination of pork was carried on by the Federal Government not as a sanitary measure but for the purpose of meeting the requirements of foreign trade, it was found that the percentage of trichinosis in hogs in this country varied from one to two. Hogs from certain localities furnished a much larger and those from other localities a much smaller percentage. Notwithstanding the rather wide prevalence of trichinosis among hogs in this country, there is but little danger from infestation in man if proper precautions are taken; indeed, this danger may be entirely eliminated if pork is not eaten until it has been thoroughly cooked or thoroughly cured. Since there is an opinion abroad that the federal inspection of meat eliminates wholly the possibility of trichinous infestation, we shall quote the following from Ransom, Chief of the Division of Zoology of the Bureau of Animal Industry:

“Microscopic inspection of pork (examining certain portions of the carcasses of slaughtered hogs with the microscope and condemning carcasses in which trichinae are found), on account of the danger of overlooking the parasites in many cases when they may be present, has not proved to be an effective means of preventing trichinosis in countries where it has been employed. Although the chances of infection are greatly reduced through the condemnation of many trichinous hogs which would otherwise be placed on the market, microscopic inspection in another way favors the occurrence of trichinosis by creating a false feeling of security in the minds of the public, many

persons believing themselves perfectly safe in eating raw pork if it has been inspected and passed as free from trichinae. The experience of Germany, where a very elaborate system is in operation, with a force of inspectors variously estimated at 25,000 to 100,000, fully demonstrates that microscopic inspection is not successful as a means of barring trichinous pork from market. Out of the 6,329 cases of trichinosis occurring in Germany between 1881 and 1898, 2,042 cases (over thirty-two per cent) have been traced by Stiles to meat which had been inspected and passed as free from trichinae. In numerous instances trichinous pork has been microscopically examined as many as 20 or 30 times before the parasites were found, and as it is utterly impracticable to make so many examinations, the unreliability of inspection for trichinae should be obvious to all. Since its uselessness as a sanitary measure is evident, microscopic inspection is not included in the system of meat inspection followed in this country. Consumers should understand that the Government mark 'U. S. Inspected and Passed' does not guarantee that the meat has been inspected for trichinae. In all cases, therefore, whether pork has been inspected or not, it should be thoroughly cooked or thoroughly cured before it is used for food."

Dracunculus medinensis or guinea worm infestation.—This disease, under the name dracontiasis, has been known from most remote times. Castellani and Chalmers think it is probable that the fiery serpents which are said to have attacked the children of Israel in the desert were guinea worms and that the serpent attached to the stick was an illustration of the method then employed for extracting this parasite from the body. The disease is mentioned by Plutarch, and Galen describes it under the name we now employ. Paul, of Aegina, states that there were in upper Egypt worms called "dracunculi," which were found in the muscles of the limbs of men and which moved and finally sought an exit by burrowing through the cuticle. He advises that as soon as the head protrudes it should be fixed or attached to a stick or piece of metal, and, while the parts are kept irrigated by hot water, the worm should be gently pulled out. He states that if during this procedure the worm breaks there will be much pain. The first to scientifically study this disease was Fedschenko, of Turkestan, who, in 1870, discovered that this worm becomes a parasite in a species of cyclops, a fresh-water crustacean. Fedschenko believed that the worm enters the cyclops by piercing and traversing its integument. Later observations by Manson, Blanchard and Wenyon have shown that the cyclops swallows the embryo worms. The latter then pierce the stomach walls of the cyclops, escape into its body cavity, and may kill the crustacean. In 1907 it was shown by Leiper that man becomes infected by swallowing water containing the cyclops. In the human stomach the crustacean is killed, probably by the hydrochloric acid of the gastric juice, and the enclosed worms are set free. The worms then bore through the walls of the stomach and develop into adult forms, some of which may measure as much as 30 inches in length. Turkhud reported that a man who drank water containing infected cyclops on April 5, 1913, first showed the presence of

the worm in his body on March 18, 1914. The adult female apparently wanders about through the body seeking opportunity to pierce the skin and reach the surface where she may discharge the contents of her uterus. In the large majority of instances the worm travels downward and makes its point of rupture through the skin in the lower extremities. In males the point of presentation is occasionally in the scrotum. In both sexes it is more rarely in the upper extremities, on some part of the trunk and very rarely about the face or head. Breaking through the skin is accomplished by the secretion of some irritating digestive substance and is often accompanied by slight fever and by urticaria. At first the epidermis over the head of the worm is elevated and this is followed by the formation of a blister which finally ruptures, disclosing an erosion which may be from three-fourths to one inch in diameter. At the center of this erosion there is a minute opening and through this the head of the worm is slowly and hesitatingly protruded. From the head there is exuded a fluid which is at first clear and then cloudy. Finally, the uterus of the parasite is extruded through the head and may extend beyond the surface as much as an inch, when it suddenly fills with a whitish fluid, ruptures and discharges its contents. In other instances there is no visible protrusion of the uterus and the milky fluid is discharged from the bottom of the erosion. A microscopic examination of this milky fluid shows it to contain numerous embryos, actively moving. The discharge of these embryos from the guinea worm is encouraged by douching the sore with water. The purpose of the female apparently is to discharge her brood into water. Some observers have remarked that the application of cold to the skin of the host about the erosion stimulates the worm to discharge her uterine contents. After successfully disposing of her embryos the mother apparently dries up and gives no further inconvenience.

Castellani and Chalmers have the following to say concerning the symptomatology of dracontiasis:

“The worm as a rule produces no symptoms until a little vesicle appears on the skin, or the outline of the worm is noticed under the skin, but urticarial eruptions have been observed by several authors and ourselves. The little vesicle bursts, leaving a round hollow, out of which exudes a clear fluid full of larvae, and at the bottom of which lies the vaginal orifice of the worm. After discharging a certain amount of fluid, the anterior end of the worm extrudes through the skin opening, and is either twisted on a stick or fixed in position by a piece of string by the native patient. It is not advisable to pull vigorously on the protruded piece of worm, as it is liable to break, and if this happens a serious inflammation of the affected area may result. The wound usually quickly heals after the worm has finally been extracted. The usual site for it to appear is about the feet or legs, more rarely the hands or arms, still more rarely the head or trunk. But all cases are not so simple, and aching or dragging sensations, sometimes accompanied by rigors and fever, may occur. Rarely it enters a knee joint,

and causes synovitis or arthritis. Usually there is only one worm, but there may be more."

A French surgeon, Emily, injects into the body of the worm when it protrudes through the erosion a few drops of a solution of bichlorid of mercury 1-1000. This apparently kills the worm and renders its extraction easy. In some instances it is possible to see the worm through the skin and to puncture its body and make an injection anywhere along its length. Macfie has employed intravenous injections of tartar emetic and states that four grains of this preparation thus used is sufficient to kill the worm in both its adult and embryonic stages.

Protection against guinea worm infection lies in the sterilization of drinking water. It seems that both the worm and its host, the cyclops, are destroyed at relatively low temperatures. Leiper states that passing steam into wells so as to raise the temperature of the water to 65° C. is sufficient to destroy the worm and its carrier. For this purpose he employs a portable steam generator which travels through the infested country and is used on every form of water-supply. The guinea worm is at home in certain parts of India, in Persia, Arabia, Turkestan, the west coast of Africa, and tropical Africa. Apparently, in recent years it has gained a foothold in Brazil (Feira de Santa Anna). The guinea worm lives but a very few days in clear water, while in muddy water it may retain its vitality for as many weeks. It will bear marked drying, but is brought back to life upon the application of moisture. According to Liston, one hundred per cent of the village wells and tanks in Dahomey contain the cyclops. This investigator thinks that there are several species of the cyclops which serve as hosts for the guinea worm.

Ankylostoma and filariae are nematode worms, but they are discussed with the diseases which they cause.

Bibliography

- BAYLIS, H. A.: Parasitology, 1920, xii, 253.
HIRSCH, A.: Handbook of Geographical and Historical Pathology, 1886, ii, 303.
LEIPER, R.: Jour. Trop. Med., 1916-1917.
RANSOM, B. H.: Bureau of Animal Industry, Circular No. 108, 1907.
STEWART, C.: Parasitology, 1916-1917.
STILES, C. W. AND FRANKLIN: Bulletin Bureau of Animal Industry, No. 35, 1902.

CHAPTER XIX

HOOKWORM DISEASE

Ankylostomiasis; Uncinariasis

Etiology.—This condition is due to the presence of a parasitical worm in the small intestine. There are two species of this parasite. The first, known as *Ankylostoma duodenale*, was discovered and described by Dubini in 1843. The second, known as *Uncinaria americana*, was described and named by Stiles in 1902. Later, Stiles suggested the name *Necator americanus* (American Murderer) for the second species. The ankylostoma is also known as the old world hookworm, and the uncinaria as the new world hookworm. However, as is now known, both species are found in both hemispheres; and it is probable that the so-called American species came from Africa. The following description of ankylostoma is taken from Braun's work on Animal Parasites:

“The body is cylindrical; attenuated anteriorly and of a light reddish color. In the oral cavity, on the ventral surface close behind the orifice, there are four hook-like teeth directed backwards; on the dorsal surface there are two teeth directed forwards; in the base of the oral cavity there is one tooth directed forwards on the dorsal surface, and two chitinous lamellae spreading leaf-like on the ventral surface. The males measure 8 to 10 mm. in length, 0.4 to 0.5 mm. in breadth; the bursa has two large lateral and one small dorsal alar processes; the rib of the latter terminates in two tridentate points; a curved rib directed backwards arises from each side of the trunk of the central rib; each lateral wing is supported by four ribs; the two spicules are long and slender. The females measure 12 to 18 mm. in length, the caudal extremity has a small spine; the vulva is somewhat in front of the posterior quarter of the body. The eggs are elliptical and have thin shells; they measure 0.055 to 0.065 mm. in length and 0.032 to 0.045 in breadth, and are laid in a state of segmentation.”

The *Uncinaria americana* is easily distinguished from the *Ankylostoma duodenale*. The former is shorter and more slender, the male measuring from 7 to 9 mm. in length by 0.3 to 0.35 mm. in diameter. The oral cavity is smaller, and instead of four ventral hook-like teeth, is provided with a pair of prominent semilunar plates. The dorsal tooth is also represented by a pair of slightly developed chitinous plates. The outlet of the dorsal head-gland, usually known as the dorsal rib or tooth, projects into the oral cavity. In the buccal capsule are pairs of dorsal and ventral submedian lancets.

While the ankylostoma is larger than the uncinaria, the eggs of the latter are larger than those of the former, measuring from 64 to 75 microns in length by 36 to 40 microns in breadth. The eggs of both species are ellipsoidal.

The life-history of these two parasites is identical and is well known in every particular. For practical purposes there need be no distinction between the two species and we shall refer generally to this parasite in the singular. It passes its parasitical existence in man and in a few anthropomorphous apes. It is harbored by no other animals and man is essential to its continued existence.

The fully developed worm is found only in the upper part of the small intestines of man. Here it attaches itself to the mucous and sub-mucous membrane, from which it draws its nourishment. The sexes copulate in the intestine, and the female discharges eggs already partially developed or in the segmentary stage. The eggs never hatch in the intestine. There is no multiplication of the organism during its parasitical life. It follows, therefore, that if there be only one infection it can continue only so long as the original individuals live. Exactly what this period is it is difficult to positively determine, because in most countries where hookworm disease prevails the individual is repeatedly infested. The greatest possible life for one generation of parasites in the intestine is believed to be somewhere about six years. The eggs are constantly being discharged from the females in the intestine and pass from the body in the feces. They are hatched in the soil, liberating the larvae. For the process of hatching, heat, moisture, and shade, are essential. Complete desiccation quickly destroys the eggs. The optimum temperature for incubation is from 25° to 35° C. Low temperatures prevent hatching, and it is generally stated that freezing kills the ova: however, Oliver states that he froze infested feces and then gently thawed it, after which the larvae appeared on the sixth day. He also kept such feces ten weeks at from 15° to 17° C., during which time there was no segmentation: but when the temperature was raised segmentation proceeded and developed larvae more vigorous than those hatched immediately. It is quite certain, however, that prolonged cold, as that experienced in our northern winters, completely kills the ova. For that reason hookworm disease is not prevalent in northern portions of the temperate zone except in places where the soil is more or less constantly warm, such as in deep mines, in brickyards, and about furnaces. Direct exposure to sunlight kills the ova. Diffuse daylight checks their development and they find the best conditions in dark places. The presence of oxygen is also necessary in the hatching of the eggs. For this reason the eggs on the surface of stools develop quickly, while those protected from oxygen in the interior of the hard feces may remain without further segmentation quite indefinitely. The eggs will not hatch under water. Frequently it happens that the stools are sufficiently dilute to prevent the production of larvae. Ashford and

King found the coffee plantations in Porto Rico ideal places for the development and spread of hookworm disease. When they began their work, privies on these plantations were practically unknown. Coffee trees must have protection from too much sunlight by larger growths. The workers deposited fecal matter widely over these shady plantations, the frequent rains kept the ground moist, the trees furnished the shade, and the whole surface of the earth was filled with larvae. The larvae as they escape from the eggs are from 0.2 to 0.25 mm. long and 0.01 to 0.017 mm. thick. They are highly motile and markedly tenacious of life. They come into being with a small amount of food substance in the form of granular particles in the glands of the intestines. Upon this material they may live possibly for five or ten days. This is shown by the fact that when placed in distilled water the granular particles may be seen, under the microscope, to gradually disappear, and life terminates in the above mentioned time. They do not move freely in water but either sink to the bottom or crawl up any projecting object, thus getting out of the water. They have been found upon wet timber supports in mines at a height of one meter above the floor. Likewise, they have been seen in the cracks between boards of bath houses.

Under the most favorable conditions the eggs may hatch within from one to three days. Within from two to five days after hatching the larvae first molt or shed the skin. There is no change during this process in shape or size. A new skin forms under the old, and during this stage the larvae grow both in length and thickness. The second molting or ecdysis occurs within from five to nine days. In this stage the old skin still surrounds the body while the new skin is being formed. The appearance presented during this molting has been interpreted as a stage of encystment. After this there is no further growth outside the host and the larvae are ready for transference to the intestine of man. In this so-called "ripe" stage they seem to be able to live on nothing and continue to live quite indefinitely. Cort and his co-workers, studying the problem on the Island of Trinidad, came to the conclusion that the generally held belief that infective hookworm larvae may live in the soil for long periods is not true, having experimented with different kinds of soil, especially clay loam, sand, and clay loam sod. The soil was kept constantly moistened and there was a daily range of temperature from 74° to 94° F. Sheathed larvae were placed on the surface of these soils and the rate of reduction was observed. These experiments showed a very rapid decrease in the number of larvae, amounting in some instances within three weeks to ninety per cent with a total disappearance in about six weeks. They have been found in the mud of mines ten months after the mine had been closed.

Oliver kept them in water under a vaselin seal and found them alive after eleven months. It should be clearly understood that neither the eggs nor the unripe larvae can grow in the human intestine and would do no harm when swallowed. The eggs liberated in the intestines never hatch in that location, nor would they do so if collected from the feces and directly swallowed. Likewise, infection would not result from swallowing unripe larvae. An extracorporeal development is an essential link in the life-cycle. The whole time required outside the human body for the hatching of the egg and the development of the larvae to the ripe stage, when it is ready to be transferred to a host, measures from five to seven days.

Avenues of Infection.—There are two avenues by means of which the ripe larvae find their way into the intestines of man. The most direct of these is through the mouth by swallowing. This, however, occurs very rarely. As has been stated, should one swallow feces containing eggs and unripe larvae there would be no development of the worm in the intestines as a consequence. The ripe larvae must be swallowed, and this occurs only exceptionally. Ashford and King make the following statement concerning direct infection through the mouth:

“Soiling the mouth with muddy hands at meal time; eating muddy vegetables and fruits; drinking muddy water; drinking from muddy receptacles; inadvertently swallowing muddy water while bathing in streams; earth eating; carrying muddy clothing home to soil the hands of wife and children; cleaning of muddy feet and transferring the infection to the finger nails; crawling of children in earth which they frequently eat; handling of mud-bedraggled dresses before meals; eating of sweets made in dirty, muddy houses; drinking of guarapo, the expressed juice of sugar cane. This list comprises by no means all of the possible modes of infection by the mouth.”

The direct infection by the mouth through swallowing of the ripe larvae may occur, as has been demonstrated, by direct experiment in man. It has been found that within from five to six weeks after introduction by this avenue, the parasite has established itself in the intestine, has become sexually mature, and has engaged in the reproduction of itself through eggs. Drinking water as a source of infection cannot be altogether ignored, but it is rather remote, considering the fact that the larvae sink to the bottom very rapidly and completely. The possibility of introducing the larvae in salad and similar uncooked foods is greater. The swallowing of dried earth would have no effect, and we must conclude that Ashford and King have quite thoroughly summed up the most probable chances of direct infection through the mouth.

The second avenue of infection is through the skin. The ripe larvae can easily penetrate the unbroken skin. Certain skin lesions, under various names, such as, “ground-itch,” “toe-itch,” “mud-itch,” etc.,

are known in all countries infested with hookworm. The ripe larvae existing in mud through which the barefoot boy or man wades, almost immediately penetrate the skin. Myriads may within a few minutes find their way into the body. This has been abundantly demonstrated by direct experiment made by Ashford, King, and Igaravidez, constituting the Porto Rican Commission on Uncinariasis, by Smith, of Atlanta, and others. These investigators have found that if a bit of mud or a drop of water infested with ripe larvae be placed on the skin and left in this position for a few hours, then thoroughly removed, the skin under the application will redden; and in a short time after this a papular eruption will appear accompanied by itch and followed by the development of pustules. For instance, Smith placed mud containing ripe larvae on the arm of a man not previously infested. The mud poultice was allowed to remain one hour. In eight minutes after the application was made itching was complained of and on removing the poultice a macular eruption was present. The next day the wrist was swollen and on the second day the eruption had become vesicular and caused intense itching. On the fifth day the vesicles had become confluent and the axillary glands were enlarged and tender. On the eighth day there was some sore throat with fever. Following this there was occasionally an unusual feeling in the stomach. Hookworm eggs appeared in the stools during the seventh week after the application.

Numerous experiments have been made upon animals, and the course of the parasite after penetration of the skin has been traced. The ripe or encysted larvae penetrate tissue of almost any kind with wonderful rapidity and soon reach the blood stream where they are carried to the right side of the heart, from which they pass to the lungs. Having reached the pulmonary capillaries, which are too small for their transmission, they again penetrate the tissue and pass into the bronchial tubes. From the bronchi they are brought by the action of the ciliated epithelium and by coughing into the trachea and the mouth. Having reached the oral cavity they are swallowed, pass through the stomach, and take up their residence in the duodenum and jejunum. No doubt if the saliva becomes contaminated many of the organisms are expectorated. Those who have had ground-itch should be instructed not to swallow their sputum. The ripe larvae are not affected in any way by the gastric juice and four or five days after reaching the small intestine they again molt, and in doing so are furnished with a buccal capsule. By means of this apparatus they fasten themselves to the mucous membrane and begin to feed upon that tissue. Four or five days later the last molting or casting off of skin is begun, after which the worms grow rapidly and within from six to eight weeks after entering the body they begin to lay eggs which are discharged in the feces.

It will be seen from the above that every step in the life of these parasites is known. When applied to the skin of the lower animals ripe larvae penetrate the tissue, reach the blood, and are carried to the heart and lungs where they develop and may cause death. Ashford and King made application of a culture to the shaven but unbroken skin of a young guinea pig which died three hours later. Examination showed one lung solidified with blood, while the other was marked by hemorrhagic spots. In these tissues, as well as in the blood, numerous larvae were found.

History.—A rather far-fetched attempt has been made to show from the Ebers Papyrus (1550 B.C.) that this parasite was known to and afflicted the ancient Egyptians. It is quite certain that the great pioneer health officer, Moses, understood the danger that lies in unburied feces. He issued the following sanitary regulation:

“Thou shalt have a place also without the camp, whither thou shalt go forth abroad; and thou shalt have a paddle among thy weapons; and it shall be, when thou sittest thee down abroad, thou shalt dig therewith and shalt turn back and cover that which cometh from thee.” (Deuteronomy xxiii, 12-13.)

Whatever precautions Moses and others may have taken, the hookworm has continued its existence and is now found all around the world in the tropical and subtropical belts from 36° north to 30° south of the equator. The magnitude of the problem will be understood when it is stated that more than half the population of the world lives in this area. In colder climates it is found in the soil only in deep mines, about brickyards, charcoal ovens, and other places where the soil is kept at a relatively high temperature.

It is an interesting fact that our short and decisive war with Spain opened up at least three important medical and scientific problems. Following this war came the epoch-making discovery of Reed and his associates of the transmission of yellow fever by a certain mosquito. As a result of the discovery Cuba was freed from this disease and the building of the Panama Canal was made possible. The wide prevalence of typhoid fever in our own army during that war led to an investigation which demonstrated most fully that this disease is disseminated not only by water and milk, but by flies, and especially that it results from contact. So great was the impetus given to the study of typhoid fever that investigations did not stop until it was shown by combined sanitation and vaccination the disease can be completely eradicated. Soon after the American occupation of Porto Rico and while that Island was still under military control, the “anemia” so prevalent among the inhabitants, was shown by Ashford to be due to hookworm infection. In 1899 the population of Porto Rico was 953,243, with a density of 264 to the square mile. Only 8.7 per cent lived in towns of over 8,000

inhabitants and the total urban population in all towns of 1,000 or over was 203,792, leaving 749,451 living in villages and in the country. Many of the country dwellers were highly respectable and lived in good houses in relative comfort. The working classes on these estates, known as the "jibaro," constituted the large mass of country people. Ashford says the jibaro is a squatter and does not own the land upon which he builds his modest house, which is a framework of poles with walls of the bark of the Royal palm, and with a roof of the same material or of tough grass which is used for thatching. Generally the floor is well raised from the ground on posts, and the family is truly a poor and miserable one which is content to have an earthen floor. The ordinary house has but one room and accommodates five or more persons. The diet of these people is of the scantiest kind. The man of the house is employed largely on the coffee plantations. He goes half-fed, poorly clothed, with bare feet, and deposits his excretions anywhere in the bushes. These excretions are loaded with hookworm eggs. Conditions for their hatching are most favorable with optimum temperature, shade, and moisture. Ground-itch, known locally as "mazomorro," is annual and almost universal among these people.

Ashford gives the following interesting and sympathetic description of the Porto Rican peasant:

"The jibaro, mountain bred, avoids the town whenever possible, avoids the genteel life of a higher civilization to that of his own. He instinctively tucks his little hut away in the most inaccessible spots; he shrinks from the stranger and lapses into stolid silence when brought face to face with things that are foreign to his life. He does this because he has been made to feel that he must do all that he is told to do by established authority, and he knows that this authority never takes the trouble to look for him unless it expects to get something out of him; because he is suspicious of outsiders, having been too often led astray by false prophets and disappointed by broken promises; because he realizes that he is not a free agent anywhere save in the mountain fastnesses. In other words, he seeks liberty in his home, freedom from the constant repression of those he recognizes as his superiors, and exemption from a repetition of deceptions that have been so often practiced upon him. He has always been made to stay strictly in his class, in the 'jibaro' class. Frequently when he tries to express himself he is laughed down, frowned down, or growled down. 'Tu eres un jibaro' is not a term of reproach exactly, but it means, 'You are not in a position to express yourself for you are only a mountaineer. You know nothing of our world; you are still a child. Your place is under the shade of the coffee tree; the mark you bear is clear to everyone; you are a "jibaro".' Thus there is a great difference between those who are jibaros and those who are not jibaros, i. e., those who live in towns or those who command in the country. This distinction is neither made unkindly nor roughly. All the Porto Rican people are kindly and they love their 'jibaros,' but nevertheless they treat them as though they were children. And the jibaro loyally follows his educated, emancipated fellow citizen, perfectly satisfied to be guided as the latter sees fit.

"Much of this guidance is excellent, and it is not our mission to seek to break down

barriers which today may be needful. The jibaro is respectful and obedient, fearful of the law and never defiant of his superiors; he is generous to a fault, sharing with any wayfarer his last plantain; he is devoted to his family and to his friends. Had he been ill treated by the educated and controlling class in the island he would be sullen and savage, but this has not been the case. If it is true that the jibaro is in many ways differentiated from the upper classes it is equally true that there is no masonry so strong as that existing among the jibaros of Porto Rico. Bound to each other by the most intricate ties of relationship and by a still more potent one, the eternal bond conferred by the title 'compadre' or godfather, they share their troubles and shield each other as though they belonged to one great family. It is really wonderful to see how quickly and with what complete self-abnegation an orphaned child or a widowed mother is gathered into some poor neighbor's hut and there cared for. * * * Education will transform this jibaro into something much better or much worse, for he will not remain content as he is when he can read, write, and see the world with his own eyes. In this education the respect he bears his more fortunate compatriots, the power for good they have over him, and the confidence he reposes in them must be preserved. The labor he must perform to enrich the island must be dignified by his employer and by himself, or else the hills will be deserted and the 'jibaro' will become a vicious hanger-on of towns. Better homes, better means of communication with towns, now becoming an accomplished fact, better food, education, in which remarkable progress is being made at this day, better habits of life, especially those relating to the modern prevention of disease, must form a part of any plan adopted to improve his condition. The planter who today sees only the laborer must see in him the man whose bodily, mental, and moral development will make the plantation a success. The planter is the man of all men in Porto Rico who must begin to help the jibaro upward in order to emerge from his own present industrial depression.

"It is a specious excuse, nothing more nor less, which avers that a jibaro is born the way he is and cannot be changed at this late day, that we must await a new generation, etc. On that principle we could expect very little from the antituberculosis crusades in New York. The truth is that to change the jibaro we must convince him that he will be bettered by the change, and he is sharp enough to change then, but the gist of all is that these changes must be begun by the men to whom the jibaro has always looked for light, and this means good hard work and much perseverance, tact, and genuine personal interest. From our acquaintance with the men to whom this burden will fall we should say that they are not only sufficiently good business men to realize the benefit they would get out of a healthy laboring class, but that the innate patriotism of the Porto Rican agriculturist and the deeper underlying sympathy for his jibaro will some day bring about the reforms that they alone can make possible."

The first years of American occupation of Porto Rico were, from a sanitary standpoint, not complimentary to our nation. During the last five years of Spanish rule the annual death rate per 1,000 was 28.9. During the first five years of American government this rate increased to 33.58. During the second five years of our control the annual death rate fell to 23.33. During the first of the third five-year period it fell still farther to 20.90, being the lowest death rate recorded in that island up to the time. During Spanish rule, smallpox and yellow fever added largely to the death rate, but with American occupation these diseases practically disappeared. During the first five years of our occu-

pation there was a crisis incident to the war and a marked fall in the price of coffee. The hurricane of 1899 practically destroyed many of the coffee plantations. The output of this crop fell from about 50,000,000 pounds in 1897 to 5,000,000 pounds in 1899. This left the jibaro insufficiently clothed, out of work with nothing saved, and already sick from repeated infections in previous years. Masses of the people were at the starvation point. Fortunately, the island was still under military control and the commanding officer of the Medical Corps was Colonel Hoff, who issued to the people the following statement: "No person shall die of starvation, and no able-bodied man shall eat the bread of idleness." Still more fortunately, Captain Ashford, who was stationed at Ponce at the time, had charge of the provisional hospital for the purpose of accommodating some thousands of sick jibaros who had come and were thronging the streets of that city. With abundance of good food shipped from the United States, Captain Ashford attempted to feed these people; but he soon found that they did not care for meat and other concentrated foods but demanded the bulky diet of the hills. More seriously still, he found that the improved diet produced a diarrhea and thousands whom he was attempting to save began to flee from the city. Captain Ashford had never seen a hookworm or its ova, but his observation and studies among these people convinced him that, primarily, their trouble was some disease which could not be relieved by any abundance of food of the best quality, and like a true scientist he set out to search for the real cause. At first he suspected malaria, and with this in view made an examination of the blood of his patients. In this way malaria was excluded; but the study revealed a general eosinophilia. He remembered of having read somewhere that this condition accompanied infestation of the alimentary tract by animal parasites. Consequently, he turned his attention from the blood to the stools and found in the dejecta a picture which corresponded with that of the ova of the hookworm given in Manson's first edition of Tropical Diseases. Thymol was administered to a typical case and led to the recognition of the worms and eggs in the stool. Thus, on November 24, 1899, Ashford was able to announce the hookworm as the cause of many a pernicious and progressive "anemia" observed on the island. In the same year Ashford carried some of these worms to Washington, where they were studied by Stiles who recognized the difference between the old world and the new world hookworm.

Ashford returned to Porto Rico and continued his appeal for the relief of these people. After four years of incessant demand an appropriation of \$5,000 was made and a commission, known as the Porto Rican Uncinariasis Commission, consisting of Capt. Bailey K. Ashford of the

United States Army, Past Assistant-Surgeon W. W. King of the Public Health and Marine-Hospital Service, and Dr. Pedro G. Igaravidez of Porto Rico, was appointed. This marks the birth of the awakening of our national conscience in the duties imposed upon us in the eradication of this disease. A report of this Committee in the form of a senate document was published by the government in 1911. It contains a summary of a ten years' campaign against hookworm disease in Porto Rico, and should be read by all interested in this scourge. Ashford estimates that when this work was begun on the island hookworm disease was accountable for about 30 per cent of the total deaths.

Before leaving the discussion of hookworm in Porto Rico, it may be of interest to inquire as to how the disease was introduced into the island. The number of Indians on the island at the time of its discovery by Christopher Columbus is variously estimated by Spanish chroniclers from 60,000 to 600,000. Even the smaller number was probably an exaggeration. There is no evidence that these Indians showed any sign of physical inferiority. The Indians were divided into groups of from one to two hundred and distributed among the Spaniards for the purpose of working the gold mines. Young women were appropriated by their conquerors as concubines. The only diseases known to prevail among the Indians at this time were smallpox, syphilis, and tetanus. These, together with the enforced separation of the sexes, soon resulted in the complete annihilation of the Indian on the island as a pure race. With the extermination of the Indian slave the Spaniard saw the advisability of importing labor, and this began by the arrival on the island of the first negro slaves in 1518. The slave traffic continued until 1817. It is an interesting fact, and probably worth more than all the chronicles of the Spanish historian, that the negroes from the gold coast of Africa carried, not the so-called old world, but the so-called new world, hookworm. It is more than probable that uncinariasis secured its first foothold in the island about the date of the founding of the first sugar plantation, which occurred in 1530. An impetus to the growth of this parasite was found in the introduction of coffee into Porto Rico in 1736. The hookworm flourishes more abundantly on coffee than on sugar plantations. The cultivation of the soil of the latter, the greater exposure to the sun, and the smaller degree of moisture, are not so favorable as in the damper, more shaded coffee plantations. These negroes have also mixed quite freely with their white masters and at present 60 per cent of the population of the island are classed as white people. The jibaros belong to this class, and in 1834 were described by an Englishman visiting the island as follows:

"The common white people, or lowest class (called jibaros), swing themselves in their hammocks all day long, smoking cigars and scraping their native guitars."

In contrast to this Ashford writes:

“What if these people were merely innocent victims of a disease, modern only in name? What if the brand placed by the Spaniard, the Englishman, and the Frenchman in olden time upon the ‘jibaros’ of Porto Rico was a bitter injustice? The early reports savor strongly of those touristic impressions of the island which from time to time crop out in the press of modern America, in which ‘laziness’ and ‘worthlessness’ of the ‘natives’ are to be inferred, if, indeed, these very words are not employed to describe a sick working man, with only half the blood he should have in his body. * * * We cannot believe that vicious idleness comes naturally to the Spanish colonist, even in the tropics, for the very reason that we have seen these descendants at their very worst, after the neglect of four centuries of their mother country, and after the laborious increase of an anemic population in the face of a deadly disease, whose nature was neither known nor studied, work from sunrise to sunset and seek medical attention, not because they felt sick, but because they could no longer work. We strongly feel that these writers have unconsciously described uncinariasis. Are the Spanish people considered ‘lazy’ by those who know them? Were those Spaniards who conquered Mexico, Peru, all South America; who formed so formidable a power in the middle ages, a lazy people? Is it ‘laziness’ or disease that is this very day attracting the attention of the United States to the descendants of the pure-blooded English stock in the Southern Appalachian Range, in the Mountains of Carolina and Tennessee, the section of our country where the greatest predominance of ‘pure American blood’ occurs, despised by the negro who calls him ‘po’ white trash?’”

Dirt eating, technically known as “geophagy,” has been known in the southern states for more than 100 years. It was looked upon as a curiosity and attributed by some to a deficiency of nourishment, but by most to innate viciousness. According to Stiles, the earliest author on this subject was Pitt (1808), who described dirt eating among the poor white people and negroes and attributed it to lack of proper food. Negroes were accused of resorting to this means of undermining their health in order to escape work. Those who indulged in this habit generally denied it when accused, and indulged themselves only in private.

In 1895, Smith found ova of hookworm in the feces in a water-closet in Galveston, but he could not ascertain from whom these feces came, nor was he certain that they did not come from an animal. Stiles, having studied the eggs and parasites brought him by Ashford from Porto Rico, began a wide investigation in the southern states and soon demonstrated the extensive prevalence of this disease and the great number of people infested with the parasite. In 1909, John D. Rockefeller appropriated \$1,000,000 and appointed a commission known as the “Rockefeller Sanitary Commission for the Eradication of Hookworm Disease.” The work was begun in 1910 and has continued up to the present time. The sanitary commission has developed into the International Health Board, which is now expending more than \$2,000,000 annually in the eradication of this and other diseases. The work is no longer confined to the United States but has been extended to many foreign countries.

The chief purpose of the board is to demonstrate in each locality what can be done in the way of disease eradication and to stimulate the local authorities to take up the work themselves. It is pleasant to be able to state that in these purposes the board has been remarkably successful. For instance, in 1915 the board contributed more than 80 per cent of the money spent in certain southern states in the eradication of this disease, while the state and county furnished less than 20 per cent. In 1919 the board furnished less than 30 per cent of the money, the remainder of the expense being borne by state and county.

Effects of the Disease.—We have already called attention to the dermatitis caused by the larvae at the point where they penetrate the skin. The penetrating power of this parasite is phenomenal. They easily pass through the thickened part of the sole of the feet of the man who has never worn shoes. Indeed, Bass has shown that they may penetrate a kid glove. The most frequent point of penetration is between the toes, though it may occur on any part of the body. The hands of gardeners, miners, and even of children who make mud pies, may be penetrated by these larvae. The ankles and the legs may supply the site of the dermatitis, especially when children wade in muddy water. The itching comes on so promptly and is so intense that the individual often is in no doubt as to when and where the penetration occurred. The barefoot boy may spend a few restless nights on account of his ground-itch. The erythema becomes vesicular and the itching leads to scratching in which infection with pus germs occurs and the whole area may become a pustular mass, requiring frequent cleansings and careful dressing. Often it happens that the toes are held together by a sticky exudate. Within a few days, as a rule, every trace of the injury has disappeared. By this time the larvae have reached the heart and possibly the bronchial tubes.

It is easy to see from what has been stated that the systemic effects vary greatly according to the number of worms in the intestine and the period during which infestation continues. In light cases where there has been only one penetration and the number of worms in the intestine is small, the effects upon the individual may be scarcely recognizable; however, in most instances coming under the head of light cases, the skin is dry with a dirty yellow tinge in whites or a pastiness in mulattoes. Patients belonging to this class usually complain of disturbances in the digestive tract. There is pain in the stomach, especially after eating, with gaseous eructations and accumulations in the intestine. There is some tenderness over the stomach and bowels, and frequently there is an abnormal and eager appetite; however, there may be cases with loss of appetite, nausea, and vomiting. The circulatory system is but slightly

disturbed. There is some increase in the pulse rate with palpitation and shortness of breath on exercise. The hemoglobin in light cases ranges from 60 per cent to normal. The number of red corpuscles is normal or slightly diminished. Dizziness, with more or less constant headache, is a frequent symptom. There is marked mental apathy. The hookworm infested individual belonging to this class is mentally slow, he is indifferent, abstracted and markedly forgetful. He is inclined to sleep on every possible occasion. It is evident that both physically and mentally he is below par. As Ashford says, to his friends he is "run down;" to unfriendly eyes he is "lazy and good for nothing."

In hookworm countries it frequently happens that individuals belonging to the best classes, possessing good homes, well clothed, and abundantly fed, have light hookworm infestations. The master who brings his dependents to the dispensary for examination and treatment often resents the suggestion that his own stools be examined, but when he complies with the request it not infrequently happens that he is found to be the unconscious host of the same parasite which, in greater numbers, has debilitated his employes.

The most marked characteristics of light cases are the decreased hemoglobin, the frequency of digestive disturbances, abnormal physical and mental weakness, and general lassitude.

In moderate cases all the symptoms mentioned above are present in intensified form. The skin is dryer and pruritus, more or less general, is common. The pallor is more marked and is easily discernible on the mucous membrane. The appetite frequently is ravenous and so insistent that all kinds of indigestible substances, such as bits of sand, dirt, plaster, etc., are eagerly swallowed. Nausea and vomiting are rare. At times there are severe pains in the abdomen and tenderness over this region is quite constant. As a rule, the bowels are constipated, but at irregular intervals there is marked diarrhea accompanied by the evacuation of undigested food and odorous stools. Intestinal indigestion is prominent and often a distressing symptom. Disturbances of the circulatory system are more marked than in the light cases. The pulse is constantly rapid and weak. Palpitation is a prominent symptom and shortness of breath after slight exertion becomes distressing. Pain about the heart, generally prolonged and dull, though sometimes acute and interrupted, is in evidence. Pulsation of the vessels in the neck may be seen. Marked dizziness, ringing noises in the ears and headaches, are frequent accompanists. In moderate cases the digestive symptoms are not less than in the light cases, but the circulatory abnormalities are much more marked and are so much more serious that they overshadow the digestive disturbances. The percentage of hemoglobin runs between

30 and 60, while the red cells number between three and four million per cubic centimeter. The eosinophilia is most marked in this group of cases; the muscles are flabby and tire quickly, but emaciation is not marked. Exertion requires much effort. The patient now looks and feels sick. The mental condition is now so depressed that it shows in the facial expression. Patients belonging to this class are so plainly sick that their inability to work is generally recognized.

In marked or advanced cases the pallor of the skin is extreme, and it may be difficult to determine where the skin stops and the mucous membrane of the lips begins. The whole cutaneous surface is harsh and wrinkled. Perspiration is entirely absent or slight. The feet and ankles are often swollen. The face is puffy and abdominal dropsy is not uncommon. The appetite shows wide variations,—in some entirely disappearing, while in others it becomes ravenous and without discrimination. There is dilation of the stomach, often accompanied by nausea and vomiting. Diarrhea and constipation alternate, but as a rule the former is more persistent and a severe dysentery without blood results. The stools are foul in odor and consist of mucus and undigested food. Gaseous accumulations in the intestines are not infrequent and at times become enormous. The pulse is rapid, weak, and irregular. Pulsations in the large blood vessels in the neck are easily recognizable. The heart is dilated; murmurs are loud and well defined. Precordial pain may be sufficient to cause intense suffering. The slightest exertion causes most distressing dyspnea. A roaring noise in the head, with dizziness, often leading to fainting, makes the patient timid about leaving his bed, chair, or house. The muscles are weak and often painful. Indeed, muscular impairment may be so great as to simulate paralysis. This condition is often characterized by marked fluctuations in temperature. At one time there may be a fever and a few hours later the temperature may be found to be subnormal. The percentage of hemoglobin is below 30, and the red blood cells may fall to 2,000,000. In most severe cases the percentage of hemoglobin falls below 20, and the picture at this time may simulate one of pernicious anemia. There is marked mental confusion and manic depressive insanity occurs in some instances. Insomnia prevents rest at night and headache disturbs the day. Patients who have reached this stage may die suddenly, or life may be extinguished by some terminal infection.

It will be seen from the above that the ill effects of hookworm infestation reach every part of the body. Clinicians generally discuss the symptomatology of this disease under the following heads: (1) digestive; (2) circulatory; (3) nervous. Any and every part of the body may be affected. Before the existence of this parasite was recognized most

of the cases were classified under the general term of "anemia" and attempts were made to improve the condition of these sufferers by better food, by tonics, and other medication. Since hookworm disease is largely confined to malarial districts the two diseases were frequently confounded. It is evident that no form of treatment directed against either anemia or malaria can materially benefit the victims of hookworm disease.

Kofoed and Tucker tested one stool from each of 22,842 men at Camp Bowie, Texas, in 1918, and found 3,079, or 13.5 per cent, positive cases. It was observed by these investigators that hookworm carriers were more susceptible to infectious diseases than those free from these parasites. Morbidity and mortality from many causes showed a general correlation with the incidence of infection, hookworm being higher, as a rule, wherever that infection was high.

Eradication.—The campaign against this disease has been most thoroughly systematized by the International Health Board. Information in the form of simply worded pamphlets, by talks, lantern demonstrations, the use of the local press, etc., is disseminated throughout the infested community. It is evident, however, that by this means only a very small part of the population can be reached. A more practical and direct demonstration is required. The International Health Board has found by experience gained in various parts of the world that it is best to do this work in groups. A working staff consists of one medical director, two clerks, four microscopists, twelve nurses, and one or two helpers or caretakers. The medical director has control of his group and must be in a position to apply discipline or to reward merit without delay. For this reason all subordinates when employed are required to sign an agreement pledging themselves to follow directions or to submit to immediate discharge. The medical director endeavors to place himself in accord with the local authorities and then to put himself in touch and in sympathy with those whom it is his purpose to serve. The clerical force keeps the records, formulates and promulgates regulations, and prepares the reports. The clerks are in charge of the apparatus, drugs, and other properties of the staff. The chief microscopist prepares the specimens which are examined by his three assistants. When a positive finding is reported by one of these it must be confirmed by his chief. So simple is the technic of the microscopic examination that it is, as a rule, easy to obtain men for this work and prepare them after a little training from among the people where the work is done. The chief nurse takes a census of the people in the district, recording at the time such facts as are deemed necessary. While making these visits and taking these records the chief nurse delivers to each person a tin container marked

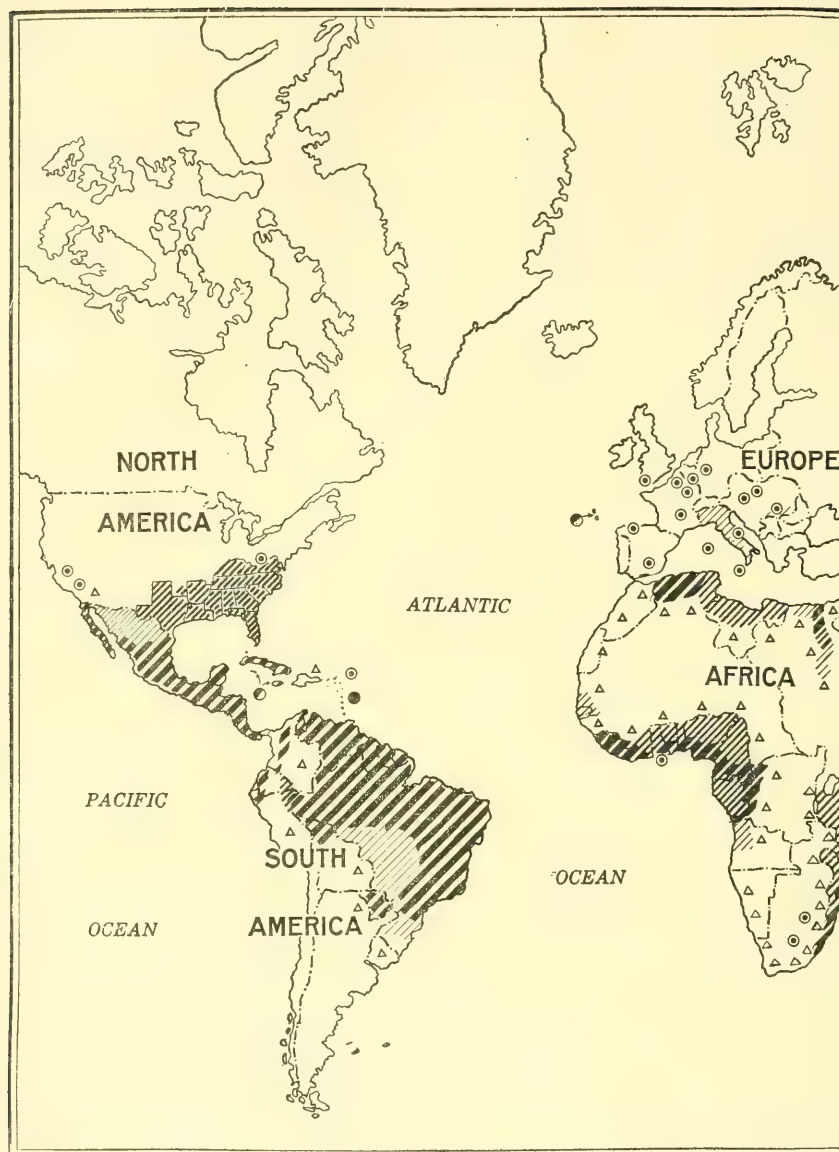


Fig. 29.

with his name, age, and location. At the same time he gives direction as to how the specimen of feces is to be placed in the container and states that on the following day the specimen will be called for. On the next day he collects his specimens. During these two visits to each house he inspects the sanitary accommodations and makes proper records. Those whose stools are found to be infested are again sought in their homes



International Health Board.

Fig. 29.

and arrangement made for the time of the treatment. Each patient is treated once a week upon the same day of the week until examination of the stool is negative. So few persons are cured by one treatment that no reexamination is made until after the second administration. It is not left to the patient as to whether he takes the medicine properly or not. Every dose is administered by a nurse. The following rules

are followed in the treatment of each patient: (1) At 5 or 6 P.M. on the day preceding the treatment a cathartic dose of sulphate of magnesia is administered. Supper is not permitted. (2) The patient remains in bed without food the following day, and at 6 A.M. takes a half dose of thymol. At 8 A.M. he takes the remainder. (3) At 11 A.M. a second cathartic dose of sulphate of magnesia is administered. This is repeated in two hours if a thorough movement of the bowels has not followed. (4) No food is permitted until the bowels have moved thoroughly and then no oily food, milk, or alcoholic drink is permitted during that day. (5) The usual habits and diet of the patient may be resumed on the day following treatment. (6) If during the treatment there is a sensation of weakness or dizziness one-half cup of strong black coffee without sugar is given. (7) During the week after the second treatment the stools are again examined. It has been found that about 50 per cent of the cases are wholly relieved of the parasites after two treatments. To those who continue to show infestation, thymol is administered weekly until the desired result is obtained.

Many anthelmintics have been tried in the treatment of this disease but thymol has stood the test better than any other drug. Thymol is but slightly soluble in water, more freely soluble in oil, and quite readily soluble in alcohol. The purpose is to prevent the solution of the thymol and to retain it in the alimentary canal. So long as this result is secured the drug is not poisonous, at least not in the doses administered. It is poisonous only when in solution and absorbable. It is on account of its solubility in oils and alcohol that these foods and drinks are not permitted while the drug is still in the intestinal tract. Various methods of administering thymol, especially as to size of dose and frequency of administration, have been tried. A method long employed in British Guiana consisted in the administration of ten grains of thymol to adults, proportionately for children, each day of the week except Sunday until negative results were obtained. By this method it is not necessary to interfere in any way with the ordinary diet of the people; however, this method has been found unsatisfactory for many reasons. It is impossible for the daily doses to be administered by nurses. There is no certainty that all patients will take the dose if it be left to them. The improvement is so slow that many become discouraged and discontinue it. Lastly, this method of treatment requires in the end a much larger amount of the drug and is more costly.

In the intensive method a dose of 60 grains of thymol is given one day of each week until the parasites are completely removed. A proportionate dose is given to children. As has been stated, the thymol is

given in two portions and is preceded and followed by cathartic doses of sulphate of magnesia.

Some precautions are necessary in the administration of this drug and all individuals receiving this treatment undergo an examination by the medical director before the first dose is administered. The following are believed to be unfit for this treatment: Those having fever of any type, diarrhea, dysentery, or gastritis; those having organic, cardiac, or renal diseases; those suffering from pulmonary tuberculosis beyond the incipient stage; those who are extremely weak or feeble from old age or other causes; pregnant women or women with serious hemorrhagic diseases of the uterus. Those having such complications should be treated for hookworm disease only under hospital conditions.

Thymol is administered in capsules, but unless mixed with some other substance it packs into lumps in the capsule which may not break up and be distributed throughout the intestines. For this reason thymol is usually mixed with an equal part by weight of milk-sugar.

Thymol is an irritant to the mucous membrane of the stomach and intestines; however, it manifests this action only slightly except in chronic diarrhea, dysentery, and related troubles. There are certain minor symptoms which may appear even when every precaution has been taken in excluding the unfit from treatment. Some complain, after the treatment indicated, of muscular weakness. This, however, is in most cases due to the abstention from food and the effects of the cathartic. When even a small portion of thymol is absorbed, vertigo and dizziness, generally of a temporary nature, may be experienced. In a few instances nausea follows the administration of thymol. This is especially true when the action of the first cathartic has not disappeared when thymol is administered. The following rules concerning the treatment of toxic symptoms occurring after the employment of thymol have been formulated by Howard, of the International Health Board: (1) Put the patient to bed and give a cup of strong hot coffee without sugar or milk. (2) If possible move the bowels with a high enema of warm water or of senna and salts. (3) If the enema does not immediately produce satisfactory results and relief does not immediately follow, give a full cathartic dose of Epsom salts or any other active saline in hot water. (4) Do not give at this time or at any other stage, castor oil as purgative or alcoholics by the mouth as stimulant.

If there should be collapse after the administration of thymol the condition is best treated by proper doses of strychnin, digitalin, or nitroglycerin.

Within recent years oil of chenopodium has acquired a favorable reputation in the treatment of hookworm disease. Weiss, of Sumatra,

gives the following detail for the use of this anthelmintic: At 1 P.M., just after the midday meal, a dose of 16 drops of oil of chenopodium is administered. At 2 P.M. and again at 3 P.M. similar doses of 16 drops are given. At 4:30 P.M. 20 grams of castor oil are given, after which the laborer returns to his quarters. No dietary restrictions are practiced nor is a preliminary purge given. The oil of chenopodium is administered in capsules freshly prepared. In the presence of a high rate of infection and all conditions which favor reinfection, it is a routine practice to administer this treatment twice yearly to all laborers, without microscopic examination or reexamination, except in certain instances.

The Uncinariasis Commission to the Orient recommends as the routine treatment of hookworm disease: 1.5 cubic centimeters of oil of chenopodium divided into three equal doses and administered at hourly intervals, the first at 7, the second at 8, and the third at 9 A.M. The commission believes in giving a light evening meal followed by a purgative dose of magnesium sulphate and a very light breakfast, consisting of milk or konje, on the morning of treatment. At 11 A.M., two hours after the last dose of oil of chenopodium has been taken, a purgative dose of magnesium sulphate is again administered. Treatment should not be repeated in less than ten days.

This same Commission treated 103 cases with thymol and 79 with chenopodium, reaching the following conclusions:

"It would appear from the comparisons given that the half-maximum dose (0.5 c.c. three times, or 1.5 c.c.) of oil of chenopodium is the treatment for recommendation as a routine vermicide.

"It does not have the toxic effects of the full dose, and two treatments have the very satisfactory result of removing 99 per cent of all worms present.

"It has the additional advantage of a more uniform action, greater effect on ancylostomes, and of being less unpleasant to take than thymol.

"Thymol shows an advantage over this half-maximum dose of oil of chenopodium in that 90 grains' dosage produces a better result when single treatments are compared. This advantage disappears, however, when two half-maximum treatments of oil of chenopodium are given.

"Smaller doses compare unfavorably with the single half-maximum dose of oil of chenopodium. A dose as large as 90 grains of thymol, if administered indiscriminately throughout the population, would probably give rise to serious symptoms."

Howard, after reviewing the relative values of thymol and chenopodium, makes the following statement:

"That oil of chenopodium will ultimately occupy an important place as a vermifuge is evident to all who have used it for this purpose. It is also evident, and becoming more so with increased experience, that it is a powerful poison, often uncertain in action with our present dosage and methods of administration. To render it safe and efficient as a therapeutic agent, more knowledge must be had as to the proper method

of its preparation, as to its chemical composition and stability, and as to its proper dosage and method of administration.”

Hall (1921) advocates the use of carbon tetrachlorid in the treatment of hookworm infection. He claims that one dose of .3 c.c. for every kilogram of body weight is sufficient to remove almost all worms. He tested this agent on monkeys, giving as much as five times the dose mentioned above, without producing unfavorable symptoms. He himself took in the morning 3 c.c. of carbon tetrachlorid and did his usual day's work without any inconvenience. Carbon tetrachlorid can be prepared cheaply and obtained quite pure. It is a colorless liquid, with a sweetish pungent taste. It is soluble in alcohol and ether and itself dissolves fatty substances. The only medical use to which it has been directed heretofore is as an anesthetic and as an inhalation in hay fever. At one time it was used by the barber in dry shampoo, but fell into disuse because a woman died suddenly after its application. There was some question as to the cause of death.

Nichols and Hampton (1922) have taken up this subject and tried it out both upon healthy people and upon those harboring the hookworm. A murderer sentenced to death volunteered to take 6 c.c. This was given one hour after the midday meal and some hours later he passed four ascaris worms. Thirteen days later this dose was repeated in the early morning before breakfast. The patient stated that during the forenoon he felt a little giddy and sleepy, but this soon passed. He was executed a week after he had received the second dose and a postmortem done one hour after death showed no worms in the intestines. Besides, the autopsy showed no lesions which could be attributed to the dose administered. In an agricultural college in Ceylon carbon tetrachlorid was tried out on the students. No purgative was given on the preceding night, all received a dose of 3 c.c. of the drug before breakfast, and no purgative was given after the drug had been administered. The students were instructed to carry on their usual mode of life and no restrictions were placed upon their work, play, or diet. No inconvenience from the drug was recognized, and an average of thirty-six hookworms for each student was recovered from the stools. Next the drug was tried on 64 additional students, with like results.

Nichols and Hampton conclude: (1) Carbon tetrachlorid is an efficient anthelmintic; (2) that the drug may be administered safely in doses of 10 to 20 minims to children of three or four years of age; (3) that it aids in the expulsion of *Ascaris lumbricoides* if it is followed by a purgative, but in this respect it is not as effective as chenopodium; (4) that the drug does not seriously deteriorate on keeping; (5) that it is preferable to chenopodium for the following reasons: (a) there is no objection to its taste; (b) it is not necessary to precede or follow its administration

by a purgative; (c) it is more efficient than chenopodium and is not so distressing; (d) it is much cheaper than any other drug used for this purpose; (e) it can be prepared in a high degree of purity and only chemically pure preparations should be used; (f) the patient is not interrupted in his vocation. A preparation of carbon tetrachlorid and ascaridol (the active principle of chenopodium) is now (1922) being made.

It is evident that the relief of individuals from their infestation with hookworms does not solve the problem of the eradication of this disease. There will always be carriers of this parasite as long as the possibility of renewed infection exists. The treatment with anthelmintics disturbs and interrupts the life of the parasite while a resident in the intestinal canal of man. In addition to the treatment of individuals, soil pollution and the opportunity for the extracorporeal growth of the worm must be dealt with. In other words, this part of the problem becomes a matter of the disposal of human excrement. Sanitary latrines must be provided and all people must use them. Moreover, such latrines must always be kept in proper condition. The fecal matter must be protected from animals, from creeping and crawling things, and from flies. It is useless to attempt, more than in a general way, a specification of what a sanitary privy should be. Nearly every sanitarian who has worked in this field has his own ideas and hobbies, and as a rule his products are satisfactory. The pail system, if properly cared for, is sufficient; but the trouble is that as a rule it is not given proper attention. The receptacles are neglected, allowed to overflow, and the excess reaches the soil. The handling of these pails is not an esthetic job and usually falls to the lot of those who are both ignorant and indifferent. In the transference of the pails the soil is likely to be polluted; in fact, it is sometimes possible to follow the track of the wagon removing the night soil by the frequent deposit of bits along the road. Then, the night soil having been brought to its destination by the carriers must be properly disposed of. It must be buried deep in the earth or emptied into a sewer or burned, and in all these processes ignorance and indifference frequently manifest themselves. Lastly the emptied pails must be disinfected, and this process is as a rule imperfectly carried out. The pail method is all right for individual families where intelligence controls, but it always has failed when an attempt is made to dispose of large accumulations of fecal matter.

The pit system is all right when properly managed. It is simpler, requires less attention, and less intelligence than the pail system. The pits should be dug deep in the earth and daily the contents should be sprinkled with lime, dry earth, or some other drying material. It goes

without saying that the pit system also needs protection from animals and from flies. On account of ground-water being near the surface the pit system is not feasible in all localities. In other geological formations solid rock may interfere with proper excavation, and besides, seams in the rock may lead to ready transfer of the material to drinking-water supplies. It is evident from this that the latrine must be selected to suit the local conditions. The U. S. Public Health Service

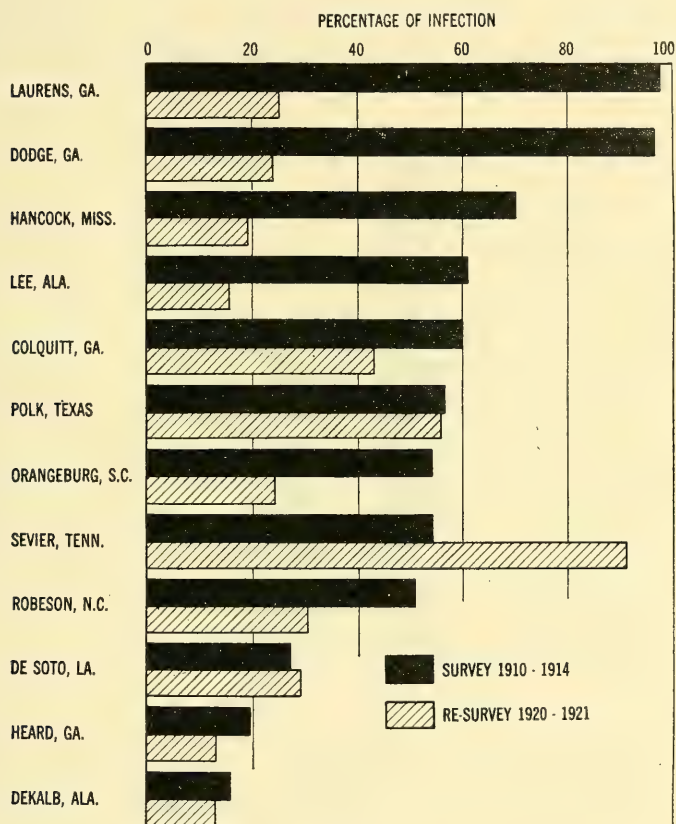


Fig. 30.

Decline in hookworm incidence in twelve counties in eight Southern States as revealed by 1910-1914 surveys and the special re-infection surveys made in 1921.

(Based on examination of 11,688 and 5,827 school children respectively.)

International Health Board.

has given much attention to this matter and some of its officers have devised different kinds of latrines suitable to different localities. At the present time this service is carrying on extensive investigations in an experimental way as to the use of disinfectants in latrines. To induce people in the mass and teach individuals to give up old customs is a slow, difficult, and tedious process. It is due to man's inborn instinc-

tive modesty that he seeks a place of privacy in relieving his body of the material from which he has drawn all possible nourishment. He has seldom thought of his excretions being dangerous to himself or to others. He merely seeks a place of privacy, and this is the only matter with which primitive man is concerned. It requires a certain degree of intelligence to enable man to appreciate the sanitary importance attending these matters. Someone has said, wittily, but not unwisely, that the culture of a nation is not measured by the magnificence of its cities, the beauty of its country, nor even by the excellence of its schools, but by the methods employed in disposing of human excretions.

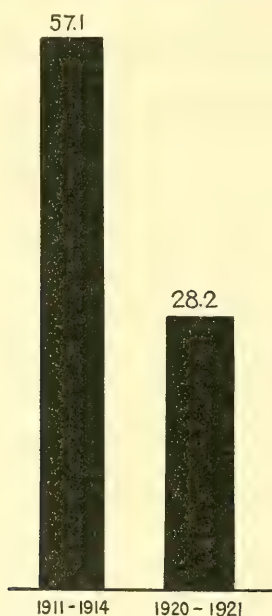


Fig. 31.

Comparison of hookworm infection rates in forty counties in ten Southern States. Based on the original infection surveys of 1911-1914 when 57.1% of 36,723 school children examined were found infected and the special re-infection surveys made during 1920-1921 when 28.2% of 21,373 school children were found infected.

International Health Board.

It is gratifying to state that in certain counties in our southern states when the hookworm campaign was begun in 1910, 90 per cent of the latrines in the county were insanitary and, indeed, were centers for the distribution of the hookworm parasite; but in 1919 in these same counties, some of them at least, 100 per cent of the latrines are sanitary. The world moves, sometimes in the right direction, but this movement is so slow that it often requires observation from two viewpoints a thousand years or more apart, to become perceptible. The sanitary regulation concerning the disposal of human excreta as promulgated by

Moses when he was leading his people from hookworm-infested Egypt will at some time in the future be fully appreciated and universally followed.

The difficulty experienced in inducing the people to use sanitary privies is well illustrated by something that occurred in a certain county in Georgia recently. Early in 1919, \$5,000 was appropriated by the Public Health Service for the installation of sanitary privies in the rural areas of this county, provided that the county authorities pledged an equal amount. This pledge was easily obtained and it was estimated that from 1,500 to 2,000 privies would be needed. Accordingly, a site was selected within the county and the manufacture of the privies begun. It was provided that the householder should pay only for the material used in construction, this sum amounting to \$10. The labor, transportation, etc., were to be paid out of the \$10,000 fund. It soon developed that many of the property owners, after getting privies at less than one-fourth their cost, lacked energy enough to build houses over them. Up to December 1, 1919, less than 200 installations had been completed. It is, however, stated by those in charge of the work that the families who have been supplied are so well pleased that in time the original program will be carried out.

Stiles, who has charge of the Commission of the Public Health Service on methods for the disposal of human excreta, states that a privy to be sanitary must protect the water-supply and it must be structurally inaccessible to animals, including mammals, birds, reptiles, mollusks, and arthropods. A single type of privy is practically an impossibility. He, therefore, recommends that certain types be practical, while others be for the time being tolerated; or, he divides them into three classes: first, the recommended; second, the permitted; third, the tolerated. He says that at the present time half of the farmhouses in the South have no privy at all; that one-third of the inhabitants are negroes, and that it is unreasonable to expect a poor ignorant negro laborer to install as good a privy as we can expect an educated white man to provide for his family. He thinks that, taking the South as a whole, we cannot hope to attain an average of 100 per cent sanitary latrines within the next decade. We are inclined to the opinion that Stiles is altogether too optimistic. In regard to the pit system he makes the following statement:

“Technically, it is a cesspool which leaks on five surfaces. Practically, with its possible maximum rating of 50 per cent, it is a stupendous advance over the existing conditions with which many of us are personally familiar; namely, southern rural conditions with an average somewhere between 5 and 10 per cent; and whether we like it or not, we must face the practical fact that this is the highest type of privy

which we can hope to have installed on about half of the southern farms for one or two decades to come."

In regard to the pail and vault systems the same authority writes as follows:

"The pail and vault systems occupy a different position from that which they held five or ten years ago. The change is due to the fact that without efficient inspection, scavenging, and disposal organization, these systems rapidly deteriorate to a surface system of 10 to 25 per cent value, and in considering this premise we are faced with a practical fact that labor is today scarcer, more expensive, and far less efficient than it was five or ten years back. The fundamental fact must be held constantly in mind that the success of this system depends upon efficient labor, efficiently administered. If the choice lies between an inefficient can or vault system on the one hand and a fairly efficient pit system on the other, my preference is distinctly on the side of the pit."

As has been stated, the International Health Board began its hookworm campaign in 1910 in the southern states. The most gratifying thing accomplished is shown in the fact that the public funds from the southern states for health purposes have quadrupled between 1910 and 1918. As the state and county funds have increased the amount of money demanded from the board has decreased. The Board began its West Indian work in British Guiana in 1914, and this has gradually extended to Dutch Guiana, Trinidad, Grenada, St. Vincent, St. Lucia, Antigua, and Jamaica. Surveys have also been made in the Barbados, the Cayman Islands, and Tobago. In all of these localities save Antigua, infection was found to be heavy, soil pollution practically universal, and general sanitary conditions most primitive. Government support of this work is slowly but constantly increasing. In Central America, campaigns have been carried out in Panama, Nicaragua, Salvador, and Costa Rica. In the last-named place the work was going nicely until it was upset by a recent revolution, as a consequence of which all health work was abated in that country and the death rate increased over 30 per cent. In 1919, Nicaragua and Salvador appropriated \$10,000 and \$5,000 respectively. Work in Brazil was begun in the State of Rio de Janeiro in 1916. During the year 1919 the Board used for its work in Brazil \$200,000, while the federal and state governments provided \$1,150,000 for rural sanitation, including hookworm and malaria. In 1916, campaigns were begun in Ceylon and in the Seychelles. In the former place, the government and planters are supplying half the funds for the demonstrations and are maintaining a sanitary organization and follow-up treatment of the infected. In the Seychelles Islands, where sanitation was practically zero, work was begun two years ago with the hope of completely eradicating the disease. The government has given enthusiastic support from the beginning. The infected area has been

covered and resurveys are in progress. In 1917, the Board provided funds and carried out a survey of Papua for the government of Australia. A demonstration in Queensland followed in 1918. A prelimi-

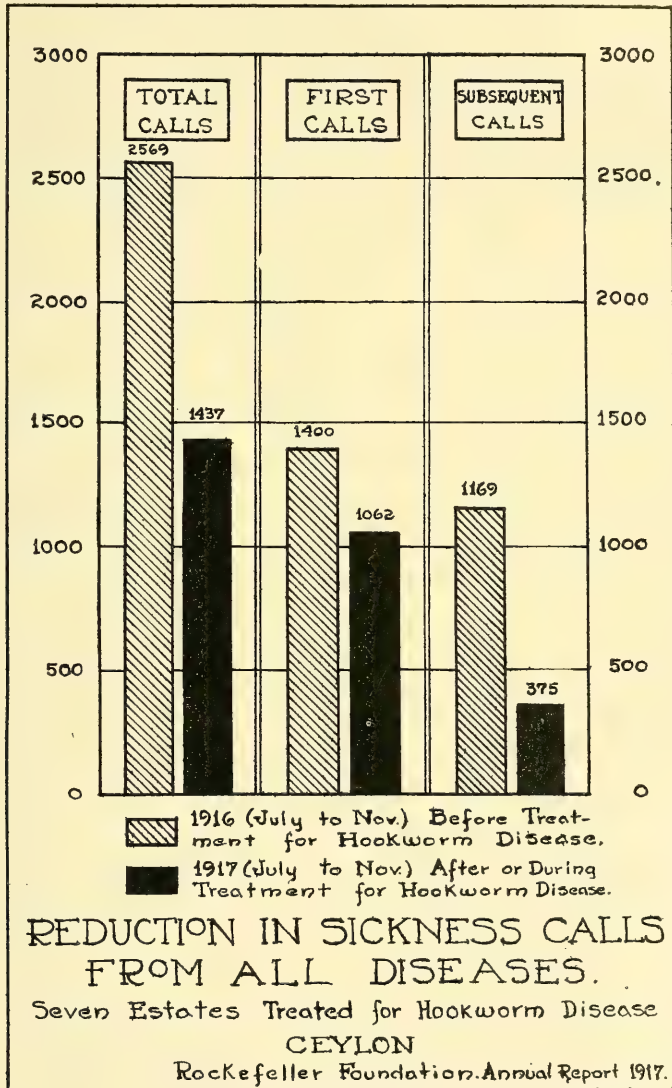


Fig. 32.

nary survey was made in Siam in 1917 and an appropriation has been made for the continuance of the work in 1920.

The eradication of hookworm is one of the grave problems that lies before the scientific world. It is a many sided problem. It involves,

not only scientific, but economic and social matters as well. Some two centuries ago a distinguished Frenchman said that if the world is to be redeemed from ignorance, poverty, and disease, it must be done by preventive medicine.

Bibliography

- ASHFORD AND IGARAVIDEZ: Uncinariasis in Porto Rico; a Medical and Economic Problem, Senate Documents, vol. 59, 1911.
DOCK AND BASS: Hookworm Disease, C. V. Mosby Co., 1910.
INTERNATIONAL Health Board Reports, 1910-1919.
SMITH, CLAUDE A.: Uncinariasis in the South; with Special Reference to Mode of Infection, Jour. Am. Med. Assn., xliii, 592, 1904.
STILES, C. W.: Public Health Reports, Reprints Nos. 110, 113, 136, 288, 418.

CHAPTER XX

FILARIASIS

Definition.—Under this name we include all those abnormalities in structure and function which result from the introduction into the body of nematode worms of the family Filariidae. These parasites appear in the bodies of vertebrates in two stages, as larvae and as adults. The latter are found in the connective tissue and the lymphatic vessels in different parts of the body. The two sexes are present and are often found in coils consisting of two or more individuals. The larvae pass into the circulating blood and may be eliminated in the urine. There are several species of filariae which may infest man and two of these may be in the same individual. However, only one species, *Filaria bancrofti*, is of pathologic importance. The presence of this parasite in man is not always accompanied by evidence of abnormality; indeed, it is often present in the blood when the bearer is not aware that he is not in perfect health. In other instances, these parasites produce more or less serious conditions incapacitating the individual to a greater extent, but seldom leading to a fatal result. Manson, who is probably the greatest authority on filariasis, gives the following abnormalities as possibly due to this parasite:

“Abscess; lymphangitis; varicose groin glands; varicose axillary glands; lymph scrotum; cutaneous and deep lymphatic varix; orchitis; chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, and elsewhere; chylous dropsy of the tunica vaginalis; chylous ascites; chylous diarrhea, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on death of the parent filariae.”

History.—The huge dimensions of the leg and scrotum in elephantiasis were observed and described by ancient Hindoo writers; indeed, the condition presents such striking abnormality that it cannot escape the attention of all in countries where it exists. The word “elephantiasis” is sufficient to indicate the grossness of the abnormality and apparently was first used by Celsus, who, however, confounded this disease with leprosy. He and subsequent authors used the same term in this erroneous way. Arabian physicians of the ninth and tenth centuries, especially Rhazes and Avicenna, described true elephantiasis of the leg by the name “da-fil” or “dau-ool-fil,” which precipitated the confusion of the two diseases. In the seventeenth century, according to Cástellani, Leonicens and Varandaeus called attention to the fact that under the term “elephantiasis” there were included two distinct diseases, and in 1709 Clark described the disease on the Malabar Coast of India under

the designation of "cochin-leg." Early in the eighteenth century, Kaempfer described endemic hydrocele as seen in India and as associated with erysipelatous eruptions on the scrotum recurring at the time of the new moon. In 1750 Hillary gave the first account of the evolution of the large leg of elephantiasis and clearly differentiated it from true leprosy. Little more than 30 years later Hendy confirmed this work and clearly traced the development of elephantiasis of the scrotum, recognizing it as the same disease that affects the legs. He observed a case of elephantiasis of the scrotum two feet in length and six feet in circumference at the base. He also noted cases of spontaneous cure by sloughing. In the first quarter of the nineteenth century Alard wrote on the elephantiasis of the Arabs, and Chapotin described the disease as it appears in Mauritius. A little later, Salese and others showed that the disease had long been prevalent in Brazil. In 1863 Demarquay, of Paris, described filarial larvae found in the fluid drawn from a hydrocele in a man who came from Havana. In 1877, Bancroft, working in Australia, discovered adult female worms in a lymphatic abscess on the arm and in a hydrocele of the cord. Since that time the name of this investigator has been attached to that of the parasite. About the same time Manson found the larvae in the lymph from an enlarged scrotum and from varicose lymphatic glands. The same author obtained an adult female worm from a case of elephantiasis of the scrotum, and a little later both sexes were found independently by Lewis and Sibthorpe. In 1878 Manson made the valuable discovery that the parasite, *Filaria bancrofti*, is distributed by a mosquito. Somewhat later the same investigator reported as to the periodicity of the appearance of the minute parasites in the blood, showing large numbers at night but disappearing wholly during the day.

In regard to the periodicity of filariae Howard makes the following statement:

"The embryos of *Filaria bancrofti* are usually in abundance in the blood of the peripheral circulation only during the night, or during sleep; during the day, or when the patient is awake, they cannot be found. There seems to be no good explanation of this periodicity, nor is it absolutely exact, but it appears to constitute a very curious adaptation of the parasite to the nocturnal habits of the mosquito which serves as an intermediary host. Manson discovered the periodicity of the embryos. He placed a patient whose blood contained filariae in a room where mosquitoes were plentiful. After the patient had gone to bed a light was placed beside him, and the door left open for the mosquitoes to enter. Later, when many mosquitoes had entered, the light was put out and the door was closed. In the morning mosquitoes filled with blood were captured, and the blood in their stomachs was examined and found to contain more filariae than an equal quantity of blood taken directly from the patient. Since then the periodicity of the filarial embryos in the peripheral circulation has been abundantly verified. In fact, as with one species of filaria the

embryos appear at night while with another they are only in evidence in the daytime and with still others there is no periodicity apparent; this phenomenon is largely relied upon for the determination of the parasite. The periodicity is to a certain degree at least, determined by the habits of the host. In the case of *Filaria bancrofti* the appearance of the embryos in the peripheral circulation seems to be determined by the decreased action of the heart during sleep, rather than by the time of day. Mackenzie succeeded in reversing the time of appearance of the filariae by inducing his patients to sleep by day and keeping them active at night. Manson found that when a patient sleeps alternately, sometimes by night, sometimes by day, the periodicity of the filaria disappears altogether. In the case of *Filaria perstans* and *F. demarquayi* there is no marked periodicity, and the absence of periodicity is given as one of the characteristics of *F. philippinensis*. The African *Filaria diurna*, which is believed by Manson and others to be the embryo form of *Filaria loa*, is present in the peripheral circulation only in the daytime. Numerous experiments with mosquitoes of a great variety of species, to determine the transmitter of *Filaria diurna*, have all proved negative, and, while a number of diurnal blood-sucking insects have been suspected, the actual transmitter remains unknown. Fülleborn and Rodenwaldt in their investigations with filariae of dogs from Italy found that there were two forms (one of them probably *Filaria immitis*) one of which showed periodicity while the other did not."

Distribution.—Castellani concludes from the fact that elephantiasis of the leg and scrotum was first reported by Hindoo writers that the original home of this disease is in Asia, from which place it passed into Africa and later was transferred to the New World with African slaves. Whatever may have been its origin, it is now widely distributed throughout the tropical and subtropical countries extending from about 41° N. to 28° S. in the Eastern Hemisphere and from about 31° N. to about 23° S. in the Western Hemisphere. In Asia it is at present known in Japan, China, the Philippines, Guam, Indo-China, Burma, Ceylon, India, and Arabia. It is seen in Australia and Oceania, especially in the Fiji, Samoa, and Friendly Islands. In America, though not common, it is occasionally seen in southern United States; much more frequently in Central America, in the West Indies, in Guiana, Venezuela, Brazil, Peru, and Colombia. In Africa it is frequent on the west coast, in South Africa, East Africa, Madagascar, Reunion, Mauritius, and northern Africa. In Europe it is said to be found, though rarely, in Spain and in Turkey. In all of these countries its distribution is uneven. It is most common along the seacoast and near the banks of large rivers, but even in these localities there are circumscribed endemic areas. It is interesting to note that at the southern end of Lake Nyanza this condition is very rare, while at the northern extremity it is common. It is, of course, impossible for it to exist where the disseminating mosquito is not found, but as is the case with other mosquito-borne diseases, the geographical distribution of the mosquito is in all probability much greater than that of the disease.

Phalen and Nichols have studied the distribution of filariasis in the

Philippines, and report an endemic center in the Valley of the Kinali River in Alba and smaller centers in Samar, Leyte, and Mindanao. They are unable to account for these endemic centers by any unevenness in the distribution of *C. quinquefasciatus*, whose presence is everywhere in evidence. It has been suggested by Wanhill, in studying filariasis in the West Indies, that there is apparently an antagonism between this disease and malaria. This author points out that while Jamaica has no filariasis, it is highly malarious; while on the neighboring Island of Barbados there is no malaria, but a high percentage of filarial infections. We are inclined to reject this explanation and attribute the comparative freedom of Barbados from malaria to the great abundance and wide employment of top minnows in the destruction of malaria.

Filarial Mosquitoes.—Unlike malaria and yellow fever, filariasis may be transmitted not only by several species of culex, but also by some belonging to the genera *Stegomyia* and *Anopheles*. *C. quinquefasciatus*, the most common house mosquito of the tropics, seems to be the most active in the distribution of this parasite. Other species of this genus implicated are *C. ciliaris* in China and *C. pipiens* in Cuba. It is possible, however, that the reporters in distant parts of the world had the same species at hand but attributed to them different names. In India and in West Africa *A. rossi* and *A. costalis* are implicated, while in Spain four species of anopheles are believed to be capable of infecting man with this parasite. In the Philippines, Ashburn and Craig, working with *Filaria philippinensis*, obtained positive results with *C. quinquefasciatus*, but only negative results with *Stegomyia calopus*.

Adult Filariæ.—This is a giant parasite compared with most of those that infest the blood. The female *Filaria bancrofti* measures from 85 to 90 mm. ($3\frac{3}{8}$ to $4\frac{9}{10}$ inches) in length, while its diameter is from 0.24 to 0.25 mm. The male is a little less than one-half the size of the female. As has been stated, the adults are found in the connective tissue or in the lymphatics of different parts of the body. In these locations they are capable of continuing life for a long time. Here they breed, the female giving birth to vast numbers of microscopic young, which are enclosed individually in a loose sheath and present the appearance of small eels. The young traverse the tissues, find their way into the circulating blood, where, as has been stated, they appear with some degree of periodicity.

Accumulations of adults in connective tissue, and especially in the lymphatics, lead to the pathologic conditions which have already been mentioned. They obstruct or may obstruct the flow of lymph, causing the enormous dilatations already referred to, and not infrequently lead to sloughing. By this process they may eliminate themselves and spon-

taneous recovery may follow. When by such a process the adults die, the microfilariae of the blood soon disappear, but what becomes of them has not been determined. They are probably eaten by the phagocytes.

Whether adult filariae interfere with the state of health depends largely upon the position they occupy. In case they do not obstruct the flow of lymph, these worms may continue in man's body quite indefinitely without recognizable ill effect. It is thought by Manson and others that accidental injury inflicted upon the female parasite may block lymph channels. In certain districts nearly thirty per cent of the people have filariasis, and most of these are quite unconscious that they are carrying a parasite. Adult worms are frequently found at autopsy when their presence had never been suspected during life. In rather rare instances the adult filariae accumulate in bundles or masses which, by their mere size, lead to the blocking of a main lymph channel. In still rarer instances, the thoracic duct may be quite dilated in places, and varicose glands and vessels due to the presence of the worms may be demonstrated. It has been shown that fibrotic changes in glands are not infrequently seen in infected persons. The blocking of the thoracic duct may be followed by congestion of the renal, lumbar and pelvic lymph channels and dilatation of the vessels. If lymphatic vessels in the urinary tract are ruptured, chyluria results. It was at first supposed that the milky opacity of the urine in chyluria is due to an excess of fat, but this has been shown to be error, and the color has been found to be due to a large amount of protein. In case the obstruction to the lymph flow is posterior to the junction of the lacteals with the receptaculum chyli, then ascites or hydrocele may follow. Strange to say, the blood in filariasis is not necessarily deficient in hemoglobin and the number of white blood corpuscles is generally quite normal; indeed, in the attacks of fever which frequently do occur in filariasis there may be a distinct leucocytosis.

It should be stated that there are still some who deny that filariae cause elephantiasis arabum, since filariae are not usually present in the blood in this condition. Manson-Bahr has the following to say on this subject:

“From this circumstance—the absence of microfilariae from the blood in elephantiasis—the question naturally arises, Why attribute this disease to the filaria? The answer to this is: (1) The geographical distribution of *Filaria bancrofti* and of elephantiasis arabum correspond; where elephantiasis abounds there the filaria abounds, and vice versa. (2) Filarial lymphatic varix and elephantiasis occur in the same districts and frequently concur in the same individual. (3) Lymph scrotum, an unquestionably filarial disease, often terminates in elephantiasis of the scrotum. (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the

lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that the elephantiasis of warm climates, with rare exceptions—the disease with which the former is so often associated and has so many affinities—is attributable to the same cause. * * * If the filaria be the cause of tropical elephantiasis, how account for the absence of the embryos from the blood, as is the case in the majority of instances of this disease? The answer is: Either the disease-producing filariae have died; or the lymphatics draining the affected area are so effectually obstructed by the filaria, its products, or its effects, that any microfilariae they may contain, or may have contained, cannot pass along these vessels to enter the circulation. Adult filariae of both sexes in large numbers may be found in enlarged fibrosed lymphatic glands—epitrochlear for example—without the presence of microfilariae in the blood stream.”

Development Within the Mosquito.—The mosquito draws the blood of an infected individual and takes the embryo into its stomach. Here the young insect molts or casts off the sheath that surrounds each individual. It then passes through the walls of the stomach and enters the thorax. In the thoracic cavity the embryo passes, according to Lebrede, through the following transformations: (1) Narrowing and invagination of the tail. (2) Invagination continues and the embryo grows shorter and wider. (3) Widening and shortening continue, and the invaginated portion forms a hyaline appendix. (4) The embryo grows and develops three lobes. From the thoracic cavity the larvae escape in the general body cavity where they manifest great activity, and finally, at least some of them, reach the labium where they await opportunity to effect a transfer to the vertebrate host.

It has already been stated that in the stomach of the mosquito, after having fed upon an infected man, the number of filariae is greater than that contained in an equivalent amount of blood drawn directly from the man. However, Fülleborn has shown that this difference is only apparent and is due to the concentration of the blood by the more rapid passage of its watery content through the walls of the stomach; in other words, this is due to the dehydration of the blood in the mosquito's stomach. This thickening of the blood serves another purpose, inasmuch as the contents of the stomach become more viscid and serve to hold the sheath of the embryo when it molts. The life-cycle within the mosquito was believed by Manson to require not more than seven days. In India it is put by James at from 12 to 14 days. In Australia, according to Bancroft, it varies greatly with the weather, generally demanding about 16 or 17 days, but in cold weather extending over 35 days. In Egypt, according to Loos, the larvae were not fully developed in the mosquito until the forty-first day after the biting. In Havana, Lebrede found that this cycle varied in time from 15 to 23 days according to the temperature.

Ashburn and Craig have made a study of *Filaria philippinensis* and its development within the culex. The intramosquito development of this parasite occupies about 14 days. In the thorax the larvae reach a length of 2.2 mm. and by this time a well-marked intestinal canal, divided into esophagus and intestine, a well-defined anus, and a mouth have been developed; in fact, the differentiation of organs appears to be complete at about the eleventh day, after which the larva elongates, narrows, and prepares for puncture of the labium. It should be remarked that there is still some question as to *F. philippinensis* being a distinct species. Some think it identical with *F. bancrofti*.

Transfer from Mosquito to Man.—To find out how this parasite passes from the mosquito to man was quite a problem. Manson followed the development of the larvae within the mosquito only to the time of their development within the thorax. He thought it possible that mosquitoes laden with these larvae fall upon water in which they undergo decay, permitting the parasite to escape, and that the disease might be acquired by drinking such water. However, after it was shown that the female mosquito is not so short lived as had been supposed, this theory became quite improbable. Bancroft suggested two theories. One presumed the accidental swallowing of infected mosquitoes, while the other provided that while the mosquito was biting the man the larvae might reenter the digestive tract of the mosquito and make its way along the proboscis and finally penetrate the human tissue. It must be remembered that all this work was done years before Ross had demonstrated the transmission of malaria or Reed the transmission of yellow fever by the bite of the mosquito. In 1900 it was demonstrated by James and others that when the infested mosquito ceased feeding upon the vertebrate it no longer contained filariae; in other words, they demonstrated that the filariae pass from mosquito to the vertebrate while the former is feeding on the latter. These experiments were made on the dog with *Filaria immitis*. Evidently the filarial parasite is too big to pass through either the esophagus or the salivary duct of the mosquito. Further study by James showed that the ripe larvae in the mosquito accumulate in the labium, but the question still remained how they pass from the labium through which there is no natural opening and how they find their way through the skin of the vertebrate. Final solution of this problem apparently should be accredited to Lebredo, of Havana. He took mosquitoes which had been infected about 28 days previously, removed their wings and legs, placed them upon a slide which he kept moist with a weak salt solution, and studied the insects and their guests under the microscope. It was easy to see through the transparent walls of the labium, and here were congregating the highly active microscopic worms. If no pressure was made not a worm escaped, but when slight

pressure was applied and the warmth intensified by the proper placing of a Bunsen burner, the larvae could be seen puncturing the outer wall of the labium and escaping from the mosquito. We shall continue Lebrido's description in his own words:

"If the head is kept up carefully and steadily we can see the embryo seeking the point, making pressure there, and finally perforating the outside at a certain point. This perforation is made quite suddenly, for we see the cephalic end jump out, as it were; the rest of the worm following slowly by serpentine movements. As soon as it reaches the fluid the serpentine movements continue, but the worm ceases to be able to advance. This remarkable difference in the results obtained by the movement indicates that the soft tissues at this stage are the natural element of the worm, and that it is prepared to move on into the human tissues directly from the mosquito. In water, on the other hand, the filariae not only cannot live, but cannot even move from place to place. In their exit the worms follow the regular order in which they occur in the labium and head. We have seen two worms making their exit at the same time. Occasionally, after two embryos have been started out, it has been necessary to warm the liquid again in order to bring other worms down from the head to the labium. Of course, after the first embryo is broken out, the others find their way out with great readiness."

We now have the explanation of how and where the parasite escapes from its mosquito host. There remained still the question of how it enters its vertebrate host. It was supposed that the filariae deposited about the wound inflicted by the mosquito made use of this opening as soon as the mosquito withdrew its lancet. This has not proved to be the proper explanation. It has been shown that the larvae deposited upon the skin of the vertebrate host easily and quickly find their way through this tissue without any help, very much as the larvae of the hookworm penetrate the skin. The larvae have been found in the skin about the wound immediately after the mosquito, having satisfied its appetite, withdraws its proboscis; indeed, the larvae may be placed upon the skin far from any mosquito bite and they will soon find their way through the tissue. Evidently, the pressure of a mosquito against the skin of the vertebrate and the warmth of the body of the latter enable the larvae to penetrate the labium of the mosquito and the skin of the vertebrate.

Other Filariae.—For more than 300 years a disease, known to the natives as *loa loa* and characterized by the presence of parasitic worms in the connective tissue, has existed along the west coast of Africa and throughout a region extending into the interior for several hundred miles. A more exact study of this condition began in the West Indies among negroes brought from Africa. There is no proof that a case has ever originated in the West Indies and, geographically, the disease, so far as we know, is confined to the African region already mentioned.

As early as 1778 a French physician, Guyot, described this parasite under its African name.

The adult male of this parasite measures from 30 to 34 mm. in length and from 0.35 to 0.43 mm. in diameter. The specimens which have been extracted from beneath the skin and from connective tissue have varied in length from 20 to 70 mm. The outer surface of these nematodes carries numerous rounded, translucent, pearly protuberances projecting from nine to twelve microns above the surface. These chitinous protuberances vary markedly in number and arrangement on individuals and are more numerous on the female. Their distribution is quite irregular. The female is longer than the male, averaging from 45 to 65 mm. The vulva is marked by a small eminence about two to three millimeters from the anterior extremity. It opens up into a vagina, which branches into two tubes extending almost throughout the length of the parasite. These tubes contain ova in every stage of development. The unsegmented egg, starting in a distant part of the tube, increasing in size and undergoing segmentation as it descends, approaches the vulva and unrolls into an embryo. These embryos constitute the microfilariae observed by Manson in this species in 1891. The embryos pass into the blood stream where they may be found in the daytime. Manson named this organism *Filaria diurna* in contradistinction to the microfilariae resulting from infection with *F. bancrofti*. Much effort has been given to distinctions between loa loa embryos and the embryos of *Filaria bancrofti*, but there are no constant differences revealed by microscopic examination.

As has been stated, the adult loa loa has its habitat in the connective tissue of man. It moves about, and in some instances its movements may be seen through the skin. Manson-Bahr makes the following statement concerning its pathogenesis:

"As already stated, *L. loa* during the period of its growth and development in man makes frequent excursions through the subdermal connective tissues. It has been noticed very frequently beneath the skin of the fingers and it has been traced from under the skin of the back, from above the sternum, from the left breast, the lingual frenum, the loose skin of the penis, the creases, the conjunctiva, the anterior chamber of the eye. Biemann says that it may wander about the body. The parts most frequently mentioned are the eyes, and although the worm may have attracted more attention when in this situation, it seems as though it had a decided predilection for the eye and its neighborhood. A patient of Manson's gave stated that the average rate at which a loa traveled was about an inch in two minutes. Both he and others have stated that warmth, such as in sitting before a fire, seemed to attract them to the surface of the body. As a rule, the movements of the parasite give rise to no serious inconvenience, but they may cause tickings, itching, crawling sensations, and occasionally, transient edematous swellings in different parts of the body. When the parasite appears under the conjunctiva it may cause a considerable amount of irritation and congestion; there may be actual pain, great discomfort with swelling and

inability to use the eye and, perhaps, tumefaction of the eyelids. Should a loa wander into the vicinity of such a situation as the rima glottidis or the urethra the consequences might be serious."

Many years ago Manson suspected the mangrove fly, *Chrysops dimidiata*, as the intermediary host of loa loa, and further studies by Leiper and others have confirmed this suspicion. It should be understood that the adult parasite may be present in the body even when no microfilariae can be found in the blood.

It is not infrequent to observe among the natives of the western coast of Africa, and especially in the neighborhood of Old Calabar, swellings the size of a hen's egg, hard, unyielding to pressure and disappearing gradually within a few days on any part of the body. These are known as "Calabar swellings." In two instances Manson aspirated the center of one of these swellings with a hypodermic syringe, with the purpose of detecting microfilariae in the extracted substance. In one instance he was successful, while in the other the evidence was negative. It is the opinion of those who have had the best opportunity to observe these swellings that they are of filarial origin. However, further studies are necessary to enable one to speak with certainty.

A German medical missionary removed tumors the size of a pigeon's egg from the heads of negroes on the Gold Coast and forwarded the preparations to Leuckart, who discovered a parasite and named it *Filaria volvulus*. Even before this, Blanchard had detected *O. volvulus* in a small tumor removed from the arm of a soldier who became infected six years earlier in Dahomey. The tumors caused by this parasite may appear on any part of the body, though they are most frequently found where peripheral lymphatics converge. Manson-Bahr says:

"In the South American form the occipitofrontal and temporal regions were noted to be most usually affected. They are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasite and encloses small cyst-like spaces filled with a greyish viscous substance consisting almost entirely of microfilariae. The position of the adult worms within these tumors is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma; consequently they cannot be extracted unless in fragments. The males lie in the little cyst-like cavities in the tumors, and can be turned out entire. The posterior extremity of the male with its copulating organs, and the anterior extremity of the female with its vaginal opening, are free and contiguous in one of the spaces."

Bibliography

- ASHBURN AND CRAIG: Philippine Jour. Sc., ii, 1.
CASTELLANI, A. AND CHALMERS, A. J.: Manual of Tropical Medicine, New York, 1913, William Wood & Company.
HOWARD, DYAR, AND KNAB: The Mosquitoes of North and Central America and the West Indies, Carnegie Institution of Washington, 1912.
PHALEN AND NICHOLS: Philippine Jour. Sc., iv, 127 and 129, iii, 293 and 305.

CHAPTER XXI

MALARIA

Ague; Fever and Ague; Paludism; Marsh Fever; Remittent Fever; Intermittent Fever

Definition.—Under the general term “malaria” we include those acute specific fevers which are caused by certain protozoal parasites designated as plasmodia. The natural habitat of these parasites is the blood of man. They are transferred from man to man through the agency of certain species of mosquitoes belonging to the family of anopheles. In the mosquito these parasites undergo a stage in their development. So far, three species of plasmodia have been recognized: *P. malariae*, *P. vivax*, and *P. falciparum*. The word “malaria” is from the two Italian words *mal* (bad) and *aria* (air). This word is an inheritance from the time the miasmatic theory of the causation of infectious diseases prevailed.

History.—We have no evidence concerning the existence or prevalence of malaria in ancient Egypt. Apparently, the Valley of the Nile has been from the earliest traditions comparatively free from this disease, and even today Egypt is not a highly malarious country; likewise, we know nothing concerning this disease in the Valleys of the Euphrates and Tigris at the height of civilization in Babylon and Nineveh, although this region is now and has been for centuries markedly malarious. In 1907 a monograph, entitled “Malaria, A Neglected Factor in the History of Greece and Rome” by Professor Jones, of Cambridge, England, attracted much attention. This author was investigating the change in the Greek character which took place during the fourth century B.C. In the course of this investigation he was impressed with the idea that malaria might have had something to do with the deterioration of the Greek at that time, and he asked himself the following questions: (1) Did malaria exist in Greece? (2) If so, to what extent was it prevalent? (3) When was it introduced, or when did it become common? (4) Is there any ancient evidence of its effect upon character?

The result of his studies led him to conclude, tentatively at least, that at the time of the height of Greek civilization malaria did not exist in that country. In Greek literature of that time he finds no reference to this disease. The word “pyretos” is found in Homer in the Iliad only once and its connection shows that it had no reference to a disease, but refers to the “burning dogstar.” After this solitary instance in Homer there

is a large gap in which no word that might possibly refer to this disease is found. It is not mentioned by Hesiod, Herodotus, or Thucydides. It is not until we come to the writings of Aristophanes (about 422 B.C.), when there appear full descriptions of the disease. Not only is malaria from this time on recognized in Greek literature, but the different forms of the disease, quotidian, tertian, and quartan, are fully and accurately described both in lay and medical Greek literature. Not only are these forms of malaria described, but attention is called to the enlargement of the spleen, which is an almost universal accompaniment to this disease. Furthermore, the relation between malaria and marshes is pointed out and emphasized. Hippocrates says that men who drink marsh water get enlarged spleens. The conclusion is that Hippocrates really observed that dwellers by marshy places suffer from enlarged spleens. His interpretation of the phenomenon which he observed was incorrect as we now know, but he evidently recognized the fact that there was some connection between marshes and malarial fevers. Hippocrates also observed the seasonal prevalence of malaria, inasmuch as he states that in autumn, quartan fevers and splenic diseases are very common.

In regard to the period when malaria was introduced into Greece, Jones writes as follows:

“It is easy to prove that malaria was present in Greece; it is difficult to find out when it first made its appearance, or when it became endemic. It is proverbially hard to prove a negative statement, and the present writer readily admits that it is impossible to show that there was no malaria in Greece before a fixed date. This does not mean that there is no evidence. On the contrary, the evidence, with respect to Attica at least, is very strong. But it is cumulative, and depends for its full force upon a due consideration of many lines of indirect testimony. In the first place, there is no reference to any disease which can be malaria, with two exceptions, before the middle of the fifth century. The first exception is the word ‘pyretos’ in *Iliad* xxii, 31. Now it has been pointed out that here the word may mean ‘heat’ merely. In any case it is not necessarily malaria. But let it be taken for granted that the word does refer to malaria, it only shows that the disease was common in Homeric times at the place where the poet lived. This was probably Asia Minor. On the other hand, Hesiod, a poet of Boeotia, which is a land especially suited for the growth of the malarial mosquito, never uses the word ‘pyretos,’ even though he might well have been expected to do so. The whole question is uncertain, but whichever interpretation of pyretos in Homer be accepted, nothing whatever can be proved as to the existence (or rather the prevalence) of malaria in those parts of the Greek world with which we are chiefly concerned.”

Jones concludes that in all probability malaria was introduced into Greece from Africa during the fifth century B.C., and that it became prevalent in that country during the fourth century B.C. As to the influence of this disease upon the Greek character, this author writes as follows:

"The effect of malaria is always disastrous. As one reads the terrible accounts given by those who have made a study of the disease, the conclusion is forced upon the mind that no nation deeply infected with malaria could have achieved the triumphs of the fifth century; and that its certain prevalence in the fourth century must have caused a decline. * * * Many, but certainly not all, of the arguments brought forward might be attacked by a clever opponent. But taken together they are very strong and it must not be forgotten that a vast amount of testimony, far exceeding that which has been offered might have been cited if the writer did not wish to exclude as far as possible all cases and symptoms which might imply either malaria or diseases of the typhoid type. It is probable that many, it is certain that some, of these were malaria. All this should be borne in mind in passing judgment upon the question. If any one is still in doubt as to the devastating effects of malaria upon character, he should consult a specialist in tropical diseases or have a few words with one who has himself suffered with the disease. His doubts will then vanish. Skepticism on the point is only possible in a land, in which happily, malaria is no longer prevalent."

Ross, the demonstrator of the relation between malaria and the mosquito, approves the conclusion reached by Jones, and makes the following statement:

"Modern Greece is intensely malarious. In the Cōpaic Plain, examined by me last year, I estimated that quite half the children were infected even in June before the annual malaria season had commenced. The Attic Plain is, and probably always was, much healthier owing to its dry climate; but numbers of other plains and valleys are certainly as bad as the one I studied. For instance, it has been estimated that in the unhealthy year 1905, out of a total population of nearly two and one-half millions, nearly a million people were attacked with malaria and nearly 6,000 died. Black-water fever, the worst form of malaria, is exceedingly common. It seems likely that malaria was introduced into Greece about the time of the Greek invasion of Africa by slaves or sick soldiers returning to their homes. It would require, say, half a century to obtain a firm hold of the country; and would then probably undermine that august civilization when at its height. Let us gaze for a moment at those magnificent marbles which have recorded forever the finest development of the human form—were these gods and heroes born out of the imagination of a people infested and degraded by malaria? * * * I find it difficult to imagine that the people who produced this great sculpture, and the no less magnificent science and literature of ancient Greece could have ever suffered very much from malaria. True, it may be said that the disease was present among them during the whole of the great age, but only to a slight degree; but this is difficult to understand, because the existence of even a few endemic cases would suffice, given the presence of the carrying agents, to produce a wide and rapid extension. Again, it may be argued that the malaria as seen in Greece today was not a cause but a result—due to the neglect of cultivation caused by the devastation of wars; but here also I may say that I have seen no evidence of the hypothesis that uncultivated lands are really more malarious than cultivated ones. All cultivation requires water, and frequently requires artificial irrigation; while the mere occupancy of cultivated land by the peasantry tends to insure the presence of the parasite—so that devastation should and does—I think, reduce malaria instead of increasing it. On the whole, therefore, it seems probable that malaria would have reached its present degree of prevalence in Greece very shortly after its introduction; and must have been the cause or a cause of the rapid decline of the country after the great age, and not the result of that event."

By a like investigation, Jones concludes that ancient Italy was free from this disease and that it was introduced into that country by Hannibal's Carthaginian mercenaries during the second Punic War, that it became quite widespread by the beginning of the second century B.C., and that it gradually became more common during the next 200 years. It is certainly true that during the first century B.C. malaria prevailed widely in Italy and even extensively in the City of Rome. Horace advised his friends to leave Rome in July in order to escape this disease, and in other places he pointed out the fact that many country districts were still free from it. In regard to the influence of malaria upon the Roman character, Jones writes as follows:

“Modern science has pronounced with no uncertain voice its judgment upon malaria as a factor in morality. ‘The effect of the disease upon the people is to unfit them for labor, to cause loss of time, loss of money, and generally to diminish their producing powers, whilst at the same time the race, if left to itself tends towards moral and physical degradation; perhaps the most incapacitating disease to which man is liable.’ Now it has been shown that malaria was endemic in Rome, probably from the time of Plautus and Terence (second century B.C.). Hence it is practically certain that the city population was gradually deteriorating. But from economic causes Rome was growing more and more congested ever since the second Punic War. The results were a sparsely populated country and a degraded rabble in the metropolis. Statesmen, perceiving the effect but not the cause, did all they could to bring back the people to the land. But economic causes were against them; the deterioration in the national character was against them, and the continuous civil wars of the first century B. C. were against them. The waste land increased, in spite of ineffectual attempts to reclaim it. The Roman people became a tainted and debased folk, penned up within the walls of the city. New blood was constantly being introduced, during the early Empire, from healthier and sounder races. Lucan, Seneca, Martial, and Quintilian, were all Spaniards. This fresh infusion was itself infected in time, and the Roman Empire at last fell to pieces. It is not pretended that malaria was the sole cause; but it is certain that the disease gave full scope to other disintegrating factors.”

It is worthy of note that many centuries B.C., keen observers detected the relationship between marshes and malaria. It is told that Empedocles (about 550 B.C.) relieved a city in Sicily from the disease by draining its marshes. As Ross says, there has been doubt thrown upon the truth of this story; but it matters little whether the story is true or not, the mere fact that such a tale was told proves that even at this early date there was some comprehension of the importance of drainage in the eradication of disease. Strabo (first century B.C.) comments on the fact that Alexandria in spite of its low-lying situation was free from marsh fever. As Jones points out, this comment could hardly have been made had it not been generally known that most places so situated were unhealthful. Hippocrates observed that those who lived in low marshy districts are neither tall nor well built, but dark-colored, bilious, and wanting in courage and endurance. Varro (first

century B.C.) actually states that there are bred in marshes animals too small to be seen but which enter the mouth and nose and cause disease. A contemporary, Columella, states that bogs breed insects armed with stings and pestilential swimming and creeping things from which come obscure diseases. Cicero and Seneca state that paludism is depopulating certain Italian districts. The use of mosquito nets is older than the Christian era. Herodotus saw them in Egypt, and Horace, Juvenal, and other Roman writers refer to them. It is stated in Roman literature that canopies were used to cover the cradles of the rich and that women recently confined spent a number of days under them.

During the middle ages if any record was made concerning this disease it has been lost. It is not likely that any advance was made, either in extending knowledge pertaining to it or in restricting its range. There has been some discussion as to whether malaria existed in the western hemisphere in pre-Columbian days. The general belief is that it was introduced into the West Indies and North America by Europeans. However, this can hardly be true in the case of South America, from which country the most valuable discovery ever made, so far as the restriction of malaria is concerned, has come. About 1640 the Countess d'El Cinchon, wife of the Viceroy of Peru, is said to have been cured of malaria by a preparation made from the bark of a tree grown in that country. This woman was sufficiently intelligent and public spirited to send the preparation to Europe and to advise its use in the treatment of the disease. It seems to have been long in the hands of the Jesuits and was known as the Jesuits' powder, especially under the control of Cardinal de Lugo. For more than 200 years there was great difference of opinion concerning the value of this therapeutic agent, because it was used in all kinds of fevers and found valuable in some and worthless in others. In some countries violent controversies arose concerning the specific effect of this agent in the treatment of fevers. It was reported in the seventeenth century that it failed in all cases at Brussels but gave relief in all cases at Delft. Of course, we now know that this meant that the fevers treated at Brussels were not malarial, while those treated at Delft were. Fabulous prices were demanded for cinchona bark and in 1658 sixty florins were paid for enough to make 20 doses. In England the bark fell into the hands of empirics and was largely advertised as a "cure-all." One of these quacks, Talbor by name, was knighted and at the same time was made physician to the King by Charles II. The real value of this or any other remedy in the treatment of malaria could not be accurately determined until the profession was in a position to make a scientific diagnosis, and this did not happen until the discovery of the parasite. The great English physician of the seventeenth century, Sydenham, seems in the different editions of

his books to have vacillated greatly in his opinion concerning the therapeutic value of cinchona bark. In the edition of his works in 1666 he stated that he had known a quartan fever to continue for several years under the use of the bark. Furthermore, it had acted disastrously upon patients when given immediately before the paroxysm but when cautiously given in the decline of the fever it had proved of some value. In the edition of 1675 he almost equaled the empirics in his claims for cinchona bark, as the following quotation will show:

"I have had but few trials, but I am sure that an ounce of bark, given between the two fits, cures; which the physicians in London not being pleased to take notice of in my book, or not believing me, have given opportunity to a fellow that was but an apothecary's man, to go away with all the practice on agues, by which he has gotten an estate in two months, and brought great reproach on the faculty."

Creighton, in discussing the controversy concerning the value of cinchona bark at that time, makes the following statement:

"The death-bed of Charles II, it is well known, was the scene of ecclesiastical rivalries; but the physicians at the bedside of the King had their rivalries too."

In 1820 Pelletier and Caventou extracted from cinchona bark the active alkaloid since known as quinin. This placed in the hands of the profession a standard therapeutic agent, but even the alkaloid continued to be used in all kinds of fevers and the discussion concerning its real value kept up. However, even these discussions were not altogether devoid of profitable results. In 1697 Morton, of London, wrote a book in which he minutely described and classified the intermittent fevers, and pointed out those in which cinchona bark proved of value. In 1717 a still more valuable work appeared from the hand of an Italian physician, Lancisi. The title of this book, "*De noxiis paludum effluviis*," shows that this author had evidently read Varro and other ancient Roman writers. He stated that among the forms of life there must be microscopic living organisms which enter the blood and there multiply. Evidently the relationship between malaria and marshy regions impressed itself more and more upon medical observers. Rasori wrote as follows:

"For many years I have believed that intermittent fevers are produced by parasites, which recreate and attack in the act of their reproduction, this occurring at more or less rapid intervals according to the species."

Metaxa, of about the same period, wrote:

"There is no objection to the belief that the parasites of intermittent fever, the first generation of which is exhausted in the first periodical attack, may go on to a second generation in the same body. * * * The duration of the attack is equal to the life of the parasites."

It will be seen from these quotations how closely medical observers by a process of reasoning approached the actual truth, which could not be demonstrated until science had made a further advance.

In our own country more than one medical observer gave good reasons for believing that the mosquito had something to do with the transmission of malaria. This was advocated by Nott, of Mobile, as early as 1848, and in 1883 King, of Washington, presented the following 19 reasons for believing that mosquitoes carry the malarial poison: (1) Both paludism and mosquitoes are connected with marshes. (2) Both require a temperature of over 60° F. (3) Both are checked at freezing point. (4) Both increase as we approach the equator. (5) Both have an affinity for dense foliage. (6) Both can be screened off by trees. (7) They can be transported by winds. (8) They are encouraged by turning the soil. (9) Are influenced by bodies of water. (10) Are diminished by cultivation, settlement, and drainage. (11) Keep near the surface of the ground. (12) Mosquitoes abound most after sundown. (13) And in the open. (14) Are destroyed by fires. (15) Are not so common in cities. (16) Are most prevalent in autumn. (17) Are arrested by mosquito nets. (18) Affect infants (which are generally protected by nets) less than adults. (19) Attack whites more than other races. In reviewing these reasons recently, Ross says that though arguments 4, 13, 14, 18, and 19 are not sound and 5, 6, and 7 are doubtful, King presents the most cogent arguments in favor of the theory of the transmission of the disease by mosquitoes.

It was quite natural for those who were convinced of the relationship between marshes and malaria to attempt to induce the disease by drinking marsh water. Many Italian experimenters carried on investigations along this line. Zeri caused nine persons to drink from 1.5 to 3 litres of marsh water a day for a number of days. In other persons he injected the water into the rectum, while he submitted still others to spray inhalation. Of course, malaria did not result from any of these treatments. Others sought the malarial poison in the air over marshes, and in 1878 it was announced that the specific bacterium of this disease had been discovered by Klebs and Tomassi-Crudeli.

In 1878 Laveran, a French Army Surgeon, then stationed at Bône in Algeria, began under difficulties the study of the blood of patients with malaria. His equipment would hardly be regarded today as satisfactory, and he did all of his splendid work without an immersion lens. He gave especial attention to the red-blood corpuscles in which black granules had been observed by Meckel as early as 1847. Upon these Laveran centered his attention, and finally was convinced that he saw in certain red-blood corpuscles parasites manifesting amoeboid move-

ments. He continued these observations, repeating them upon all patients with malaria, and in 1880 he announced that he had discovered in the human red-blood corpuscles of malarial patients a living parasite which could not be found in the corpuscles of other patients. He convinced himself that the black granules consist of excrementitious matter produced by the parasites as the result of their feeding upon the red cells. After this, the demonstration that these parasites are the actual causes of the disease was relatively easy. It only remained to inject the blood of malarial patients into healthy persons and produce the disease with all its characteristic symptoms. This was done in various parts of the world with universally positive results. It was, therefore, established that the parasites observed in the red corpuscles in persons with malaria constitute the causal agents in the production of the intermittent or malarial fevers.

In 1886 Golgi showed that these parasites reproduce themselves by sporulation, that the febrile paroxysm in the patient begins simultaneously with the liberation of the spores, and that the parasites of quartan and mild tertian are morphologically different. A little later, Canalis and Marchiafava and Celli made similar discoveries regarding the malignant parasites and showed that these differ from the quartan and the mild tertian. Danilewsky about the same time reported the discovery of similar parasites in birds and certain other animals, and Romanowsky prepared a stain by which all malarial parasites are easily recognized. It will be seen that these discoveries opened the way for the most thorough investigations of the malarial parasites, and this field has been most successfully worked, with the results that have made it possible for the world to ultimately eradicate this disease which, even today, holds a large part of its population in bondage. The discovery of the parasite was not sufficient to put man on the right road in his endeavors to exterminate this disease. It remained to be shown how these parasites are transferred from an infected individual to an uninfected one. As we have already shown, by a process of reasoning founded upon their observations, many men had concluded that this transfer was through the agency of a mosquito; but these men had had only theories, there had been no scientific demonstration. In 1889 Ross, of the Indian Medical Service, began his investigations along this line. He first studied the *culex* and the *stegomyia* mosquitoes. He tried to infect healthy persons by causing them to drink water in which mosquitoes which had bitten malarial patients had died. By some accident, he states, the first case appeared successful, but of 21 succeeding experiments all failed. He then caused *stegomyia* and *culex* to feed upon malarial patients and subsequently to bite healthy people. These ex-

periments were unsuccessful. He had not found the right species of mosquito. Moreover, the period between the feedings was too short. In 1895, employing anopheles and lengthening the time between the feedings, he succeeded in transferring malaria from person to person. As Ross says: "The problem was practically solved, only the details and formal proofs required to be ascertained."

The slowness with which the world accepts and utilizes scientific discoveries is commented upon by Ross as follows:

"Laveran's discovery of 1880 was one not only of theoretical, but of practical importance. It enabled medical men to distinguish with certainty cases of malarial fever from other diseases, and, after making the diagnosis, to treat the patient methodically. But many years elapsed before it began to be used for these purposes. The parasites were not seen in India, for example, until 1887. I did not hear of the discovery until 1888 and did not see the parasites until 1894. Scarcely half a dozen men were studying them in India at that time. The use of the microscope scarcely became general anywhere in the tropics until after 1900; and quite recently medical men have told me of hospitals which were not even provided with these indispensable instruments. Numbers of others had never read the fundamental literature; and up to the present day many colonies possess no sufficient organization for circulating recent medical papers. Yet in most tropical countries there were large public medical services which ought to have been properly provided for in these respects."

The Parasites.—It is hardly within the province of a work on epidemiology to go minutely into a study of malarial parasites. From a study of the symptomatology of malarial fevers, it was known to ancient Greek physicians that there are three types of fever, quartan, tertian, and the irregular types. The scientific explanation of these observations was elucidated by Golgi in the late eighties of the nineteenth century, who showed that each type of fever is produced by a special parasite and that the paroxysms are simultaneous with the discharge of spores into the blood. Each type of the malarial parasite requires a definite period of time for its growth, development, and reproduction. It may be well to briefly review the work done by Golgi in establishing these important facts. His first cases were persons suffering from untreated simple quartan fever with the paroxysm coming on every third day. In one of these cases in which the paroxysm was expected at noon, Golgi began examining the blood at 11:30 A.M. and found that the corpuscles contained many full-grown parasites full of spores. While the blood was being examined the attack came on. On the next day during which there was no fever the blood contained only immature parasites. On the second day, also free from fever, the parasites had grown sufficiently large to occupy from three-fourths to four-fifths of the corpuscles in which they were found. On the next day three hours before the expected paroxysm the blood was found to contain parasites, most of which had already reached maturity and some of which showed evidence

of beginning spore formation. An hour before the attack the number of these containing spores had greatly increased. The attack occurred at the usual hour, and three hours later few sporulating forms could be found; while two hours later still all had disappeared, being replaced by young parasites. In this manner Golgi studied in detail some 40 cases. Most of these were simple quartan, but some were double quartan. In the latter there are two sets of parasites, each reaching maturity on different days. The parasites of each set develop independently of those of the other set. Golgi also studied cases of triple quartan, and furthermore pointed out that there is a third variety of parasite—one which produces so-called “crescents.” These observations have been repeated by numerous investigators in various parts of the world and have been uniformly confirmed. The parasites are introduced into the blood by the bite of an infected anopheline. The parasites thus introduced penetrate the red-blood corpuscles. As a rule, in tertian and quartan infections, only one parasite is found in a single corpuscle, although exceptionally two are seen to have crowded themselves into the same corpuscle, but in estivo-autumnal infections multiple infection of the corpuscles is very common. The parasite lives within and feeds upon the blood corpuscle. On reaching maturity each parasite ruptures the corpuscle which it has destroyed and discharges its spores into the circulating blood. Each of these spores, so far as it escapes the destructive action of the blood plasma, clings to and finds its way into another corpuscle, and thus the method of propagation is continued indefinitely.

The parasites being introduced all at the same time and consisting of the same brood reach maturity and produce their spores at the same time. When first introduced the number may be so small that no visible effect upon the body results from the first one or more sporulations. The paroxysms first occur when there is enough of the poison set free to induce fever. Just what the pyogenic agent is in these fevers is not positively known. It may be a soluble substance which escapes into the plasma on the rupture of the corpuscle and the discharge of the spores, or it may result from the cleavage of a portion of the spores through the action of digestive or destructive ferments in the blood plasma. Ross estimates roughly that fever results if one in 100,000 red-blood corpuscles is involved. The same author condenses the known facts into the following statements:

(1) The parasites are not found in those who have not suffered from malarial disease. In the 40 years which have elapsed since Laveran's discovery, hundreds of thousands and possibly millions of patients suffering from various diseases have been examined for these parasites taking the civilized world as a whole, and there has never been a case reported by a competent observer of the finding of these parasites in

one who has never had malaria. In Britain, for instance, now practically nonmalarious, these parasites are never seen in the vast numbers of hospital patients examined. In the tropics they are often found, especially in children who have no fever at the time of examination; but these children have previously had or will subsequently develop some symptoms of malaria.

(2) The parasites can always be found in a large proportion of malarial cases. It should be understood that in a blood examination only a minute quantity of blood compared with the total amount in the body passes under observation, and when the parasites are not numerous they may be overlooked even by a skilled observer. In other instances the number of parasites in the blood may be so small that they are not detectable at the moment, but are likely to multiply and be more abundant and easily detectable later. In still other instances, quinin has been administered and this agent may have reduced the number of organisms without destroying all of them so that detection is difficult. However, the finding of the parasite in malarial cases depends largely upon the skill and time given to the search by the investigator. Laveran detected the parasite in 432 out of 480 cases in Algeria; Thayer and Hewetson in nearly all of 333 patients in Baltimore; Billet in one hundred per cent of 395 cases in Algeria; Duggan in every one of 400 cases in Sierra Leone; in fact, it is expected in well-equipped hospitals that no case of malaria will escape detection although repeated and careful examinations may be required in some.

(3) The patient's fever begins at the moment the spores of the parasite are liberated. We have given sufficient detail under this head in reporting the studies of Golgi in which he demonstrated that the different parasites require different periods for maturation and sporulation.

(4) The different types of malarial fever are caused by the different species of parasites. This also was demonstrated in the classical experiments made by Golgi. His findings have been universally confirmed and it is now demanded that the blood examination should not only determine the presence or absence of malaria, but if present the variety of parasite responsible for the individual case.

(5) Both parasites and the fever may be reproduced in healthy persons by inoculation with infected blood. By this means it has been demonstrated that the fever induced in the recipient of the blood is exactly the same in symptomatology with that manifested by the donor. Blood inoculations have been made so repeatedly and have been so universally successful that there can be no doubt on this point.

(6) Both the parasites and the fever may be reproduced in healthy persons by the bite of infected mosquitoes. In making this demonstration it is essential that the mosquitoes be developed from the larva in

order to be sure that they have not previously become infected. When this precaution is taken, not only is malaria transferred from one individual to another, but again it is true that the malaria in the recipient is the same form of the disease as that manifested in the original case. Anophelines bred from the larvae have been permitted to feed upon quartan cases in Italy and then sent to London where they have fed upon healthy individuals, and these people have developed quartan malaria.

These experiments, which have been repeated so often that they are no longer regarded as novel procedures, amply prove that these parasites cause the disease.

Ross estimates that about 50 plasmodia per c.mm. are necessary to produce the first distinctive paroxysm of malaria. This assumption is based upon the further assumption that the patient bears only one set of parasites. If, however, there are two or more sets, each sporulating on different days, the total number of plasmodia in the blood should, theoretically at least, be several times larger. It does not follow that if 50 plasmodia per c.mm. are sufficient to produce the first attack that an equally small number will produce subsequent paroxysms, because as paroxysm succeeds paroxysm there is undoubtedly an increase in the parasiticide action of the blood; indeed, it is a matter of observation that even without treatment the periodic paroxysms may grow less and less violent, and so far as symptoms are concerned immunity may apparently be established. This is supposed to be the explanation of the so-called latent malaria frequently observed. A man during a residence in a malarious community may have frequent attacks of the disease and finally apparently recover and then go to some nonmalarious country. Here without again being infected he may suddenly develop the disease. The reawakening of latent malaria is generally accompanied by and probably due to some untoward condition to which the individual is subjected and by means of which it is supposed that his acquired immunity is lessened or lost. It is an interesting question as to what becomes of the parasites during these periods when the symptoms of the disease are not manifested. Evidently there must remain in the body during this time, be it a few weeks or many years, a certain number of the parasites. They cannot be demonstrated by examination of the blood. We may say that either they are not in the blood or that they are not present in the blood in sufficient numbers to be detected. Because we cannot find them is by no means proof that they do not exist, and, since the disease accompanied by their reappearance develops without reinfection, we must conclude that in some form or another the parasites remain in the body through these latent periods, be they long or short. It has been suggested that during these periods of latency

the parasites are encysted in some organ; but, if this be true, the encysted forms have never been detected. Furthermore, it has been suggested that a few spores may be carried in body cells, where they lie dormant during the latent period and spring into activity when the body cells reduced in efficiency by any special stress or strain, are unable at the time to hold them in prison.

Craig has proved, by careful histologic studies made of the liver and spleen in patients dying of disease other than malaria, but who came from badly infected districts, that the plasmodia of tertian and estivo-autumnal malaria may be found in small numbers in the capillaries of these organs undergoing their ordinary human life-cycle, or schizogony, although the patients examined had never presented symptoms of malaria prior to their death from some other disease. These observations conclusively demonstrate that the malaria plasmodia may be living and multiplying in the internal viscera of man although no symptoms of their presence be noted. There are many other diseases in which the causative agent remains in the body and is sometimes easily demonstrable long after recovery from the active symptoms. In some of these also there are relapses. It seems most probable that in these instances there is a *modus vivendi* established between the foreign and the body cells by means of which a small number of the former are tolerated within the domain of the latter, apparently on promise of good behavior. We see examples of this kind not only in other protozoal diseases, but in some of those of bacterial causation. It must be admitted that the parasites in small numbers continue in the body during these latent periods, and since the life of an individual parasite is short it seems necessary to conclude that there must be during this time not only a continuance of life, but some form of reproduction. In regard to these latent periods in which there is no evidence of the disease and which Ross calls "rallies," this author writes as follows:

"Many diseases—tuberculosis, trypanosomiasis, relapsing fever, leprosy, etc.—exhibit such variations in intensity. We picture to ourselves a long struggle between the invaders and the opposing force—first one side triumphs and then the other, and death or recovery ends the contest. Just as rest and good food encourage the resistance, so, probably, anything which weakens the patient—fatigue, chill, heat, dissipation, other sickness—tends to encourage the parasites. Educated patients often declare that their fever is brought on by such causes. Military surgeons recognize that when infected troops are dispatched upon arduous military duties, numbers of them begin to fall sick at once, even though it may not be the season of fresh infections. Travelers and planters complain of the same thing as regards their porters or coolies; and medical men notice the frequency of malarial relapses after typhoid fever, venereal diseases, child-birth, accident, etc."

In this connection it may be well to call attention to the fact recorded in our discussion of typhoid fever—that when typhoid fever appears

as an intercurrent disease in one with malaria, all malarial symptoms disappear during the course of the typhoid fever but reappear after recovery from typhoid fever. Up to the present time we have no satisfactory explanation of such observations.

Since each malarial parasite destroys a red-blood corpuscle at the same time that it multiplies itself in spores and each of its numerous progeny destroys another corpuscle, it must be evident that if this operation proceeded without let or hindrance all malarial cases would terminate in death, but we know that the death rate, from the lighter malarias at least, is not high, that it is a chronic disease tending to disability rather than to speedy death. It must be evident, therefore, that as the disease develops, the body cells at the same time are not inactive but are engaged in strengthening their resistance. In malarious countries the active disease is found most frequently in children, while the adults show by their enlarged spleens and general cachexia that they have passed through the active manifestations of the disease. In the individual there is a certain immunity established to malaria. In reaching this condition of increased resistance, however, the individual has both his physical and mental strength reduced and remains more or less a cripple. It is this degrading, lasting, and almost universal impress that this disease makes upon the people that renders the necessity, or at least the desirability, of its eradication of great importance. A more acute disease with a higher death rate may reduce a population more quickly and more extensively, but it does not leave upon a people a more disastrous effect. Whatever the extent of immunity that may be established in the adult as a result of his having passed through the more active stages of the disease in his childhood, there is no evidence that the adult passes on to his children any satisfactory degree of immunity. Malaria has in all probability been almost universal in Greece for more than 2,000 years, covering at least 60 generations, and still Ross found that quite half the children in the Copaic Plain were infected even in June before the height of the malarial season had been reached.

It must be evident from what has been said that malarial diseases result in more or less marked anemia; in fact, it is not infrequent to find in malarious countries the number of red-blood corpuscles in individuals reduced to 2,000,000 per c.mm. and even to less than this number. That no one can be healthy either in mind or body with his red blood corpuscles reduced to half the normal number or even less, requires no argument. Ross raises the very important question as to the average duration of untreated infections. If 1,000 persons simultaneously infected were to be removed simultaneously to a perfectly healthy area

and were there kept untreated, how long would their infections continue? From certain statistics which he has assembled, he concludes that one-half would recover in three months, three-fourths in six months, seven-eighths in nine months, and fifteen-sixteenths in a year. We take it, however, that Ross does not mean to imply that these people would be free from the probabilities of frequent relapses, nor would the disability imposed upon them by the infection be wholly removed.

As has been stated, Hippocrates observed that those who live near marshes have enlarged spleens. This is a matter of importance to the epidemiologist, as well as to the pathologist, because with certain precautions splenomegaly is used as a measure of the prevalence of malarial diseases. Ross makes the following statements on this point:

“(1) That in a given number of infections of the same duration (a) in children and (b) in adults, the children will show a greater degree of splenomegaly. (2) That in a given number of infections of the same duration (a) in Indo-Europeans (b) in negroes, the former will show a greater degree of splenomegaly. (3) That in a given number of infections of the same duration (a) in untreated persons (b) in persons of the same age and race treated even slightly with quinin, the former will show the greater degree of splenomegaly. (4) That in a given number of infections of the same duration (a) in persons infected only once, (b) in persons who have been subject to repeated infections, the latter will show a greater degree of splenomegaly. (5) That the number of parasites tends to vary inversely as the degree of splenomegaly; that is, that the parasites tend to die out in persons with very large spleen. (6) That a hot and damp climate, or insufficient food, or certain diets, or bad drinking water, may possibly favor the development of splenomegaly; in other words, that the degree of splenomegaly may not always be an exact measure of the amount of malaria in a locality.”

Ross also calls attention to the fact that splenomegaly, even in endemic form, may be due to kala-azar. However, since the parasite of this disease and its method of detection are also known there should be no confounding of the two diseases. In malarious countries the percentage of enlarged spleen, or what is known as “spleen rate,” falls with increase in distance from marshes.

The Life-Cycle of the Parasites.—In the technical language of the protozoölogist there are two cycles in the development of these parasites. One occurs in the blood of man, is asexual and is designated the schizogonic cycle, while the other occurs in the mosquito, is sexual and is called the sporogonic cycle. The blood of the infected man contains mature sexual elements known as gametes, but copulation cannot occur in man. In the mosquito the male sexual elements, known as microgametocytes, throw off flagella, known as microgametes, and these copulate with the female elements, known as macrogametes. As a result of the contact between the microgamete and the macrogamete

(respectively male and female elements) the latter prolongs its protoplasm, forming the so-called cone of attraction. As a result of the union of the male and female elements, there is first formed the oökinete. This stage of reproduction may be observed in malarial blood on a glass slide, but outside the body of the mosquito the process of reproduction goes no further. In the mosquito the oökinete penetrates the wall of the stomach of the insect and outside the wall is transformed into what is known as the oöcyst. The oöcyst grows and divides first into sporoblasts and later into sporozoites. The sporozoites set free from the bursting oöcyst pass into the general body-cavity of the mosquito and find their way into the salivary glands, where they remain until the mosquito, through its proboscis, injects them into a human being. Having been thrown into the blood the sporozoites enter the red-blood corpuscle and are now known as schizonts. In the blood cell the schizont grows and undergoes a process of division, forming what are known as merozoites. When the blood corpuscle ruptures, the merozoites are thrown into the blood and enter other red-blood corpuscles. Coincident with these developments the schizonts also produce sexual elements, or gametes. However, the sexual elements cannot copulate within man's body on account of the unfavorably high temperature; therefore, sexual reproduction must await the transfer of these gametes to a mosquito, in which the temperature is several degrees (about 10) below the blood of man and where sexual reproduction takes place. The period required for the complete sexual reproduction in the mosquito is from 10 to 12 days ordinarily, but under exceptional conditions may greatly exceed this time. The most favorable temperature for sexual reproduction in the mosquito lies somewhere about 28° C. Below 22° C. the development of the parasite in the mosquito goes forward more slowly and may require as long a time as 50 days. During the hot months in tropical and subtropical countries the full development of the parasite in the mosquito is usually completed within 12 days. This means, of course, that a period of about this time must elapse between the feedings in order that a mosquito originally uninfected may transmit the disease from one man to another.

Anopheles.—After the discovery of the parasite by Laveran (1880) and the demonstration of its transmission by Ross (1897), it remained to be determined whether the disease can be transferred from the infected to the uninfected by other means. During the summer of 1900 two very important experiments with the idea of determining this point were made in Italy. Grassi undertook to protect 104 persons living in ten cottages and two railroad stations near Salerno from the disease by excluding mosquitoes from their habitations. Although during that summer the disease was widely prevalent among other people in the

same neighborhood only three out of the 104 persons showed any evidence of the disease, and these were evidently relapses from malaria acquired the previous year. During the late summer and early autumn of the same year, Sambon and Low, of the London School of Tropical Medicine, spent three months in a house of five rooms a short distance from Ostia in one of the most malarious parts of the Campagna. This house was tightly built and thoroughly screened. With two Italian servants these doctors lived in the house, took no precautions other than the screening and being careful to enter the house at sundown and remain there until full daylight the next morning. During the daytime they explored the neighboring swamps and woodlands and visited the villages. They received and entertained many visitors, but were always careful to shut themselves in the house before sundown. At their screened windows they stood and watched the swarming mosquitoes on the outside. During the rainy season, when practically all the inhabitants of the neighborhood were shaking with malaria, they made it a point to go out into the rain and get thoroughly soaked. At the same time they demonstrated that the prejudice against night air was unwarranted, except insofar as mosquitoes might come with the approach of night. The screened windows and doors permitted the night air to circulate freely through every room in the little house. Although surrounded in this way for three months by swarming mosquitoes they passed the time in moderate comfort, and at least remained absolutely free from malaria. During the same summer, still another similar experiment, though involving more people and being somewhat more complicated, was carried out by Fermi and Tonsini on the Island of Asinara, which is small and inhabited only by convicts and their guards and lies a short distance off the north coast of Sardinia. The results obtained in these and similar experiments did much to convince the world that malaria is disseminated only by mosquitoes. As has been stated, Ross and other observers found that malaria is not transmitted by either the *Culex* or the *Stegomyia*. Credit is generally given to Grassi for demonstrating that human malaria is transmitted only by the anopheles.

Bird malaria is transmitted by the *Culex* and the *Stegomyia* is the carrier of yellow fever, but the transmission of malaria in man seems to be the special function of the genus *Anopheles*. However, not all species of anopheles have been incriminated. Up to the present time the following species of this genus have been found able to transmit malarial parasites:

North America. *Anopheles crucians*. *A. quadrimaculatus*. *A. punctipennis*. *A. pseudopunctipennis*.

Europe. *A. maculipennis.* *A. bifurcatus.* *A. superpictus.* *A. hispaniolo.* *A. sinensis.* *A. turkhudi.* *A. theobaldi.*

South America. *A. cruzi.* *A. albimanus.* *A. argyritarsis.* *A. intermedius.* *A. punctipennis.* *A. pseudopunctipennis.* *A. pseudomaculipes.* *A. tarsimaculata.*

Asia. *A. barbirostris.* *A. culicifacies.* *A. funestus.* *A. fuliginosus.* *A. ludlowi.* *A. maculatus.* *A. maculipalpis.* *A. minimus.* *A. rossi.* *A. stephensi.* *A. sinensis.* *A. theobaldi.* *A. umbrosus.* *A. turkhudi.* *A. willmori.* *A. jeyporensis.* *A. listoni.*

Africa. *A. culicifacies.* *A. theobaldi.* *A. maculipennis.* *A. bifurcatus.* *A. superpictus.* *A. algeriensis.* *A. funestus.* *A. costalis.* *A. maculipalpis.* *A. mauritanus.* *A. pharoensis.* *A. turkhudi.* *A. umbrosus.*

Japan. *A. jesoensis.* *A. formosaensis.* *A. cohesa.*

Philippine Islands. *A. fuliginosus.* *A. barbirostris.* *A. ludlowi.* *A. maculatus.* *A. minimus.* *A. sinensis.*

Porto Rico. *A. albimanus.* *A. argyritarsus.* *A. tarsimaculata.*

Panama. *A. argyritarsis.* *A. albimanus.* *A. pseudopunctipennis.* *A. tarsimaculata.*

It must not be understood that the above is a complete list of the species of anopheles which may transmit malaria. The classification is still in process and names are frequently changed. New species are being created and, in fact, a name proper today may fall into disuse before the year is past. When Ross demonstrated that the mosquito transmits the malarial parasites numerous entomologists set out to reclassify species of mosquitoes, and this work is still in flux.

Activity.—Most species of anopheles are most active at twilight, evening and morning. Their daily period of activity seems to be limited. According to Grassi, anopheles begin to fly while one is still able to read by daylight but when it is too dark to read they disappear. According to this author, the period of activity in the evening in Italy seldom lasts more than 40 minutes. They begin to approach houses in relatively small numbers, reaching their greatest density in about 20 minutes, and then gradually decrease in number. On cloudy days they come earlier and remain longer. Apparently they are governed by the amount of light and not by the clock. The number appearing in the morning twilight is smaller than that seen in the evening. On moonlight nights, especially if there be but little air stirring, they may bite all night, but usually cease their depredations when the night temperature reaches its lowest point, which is about 2 A.M. Between 4 and 6 A.M. they may again bite in the fiercest manner. These observations were made in central and southern Italy. In more northern parts of Italy

the time of activity is much more restricted on account of the low temperature. They are seldom found flying when there is a marked movement in the air. Apparently they are not carried by the wind, nor do they face strong movements in the air. When it is windy they rest in the foliage. The anopheles seldom bite in bright sunlight, but they may bite out-of-doors during the daytime, especially in shaded places, or in houses which are not well lighted or when the day is cloudy. From observations made in Brazil by Chagas and others, it seems that different species of anopheles enjoy different degrees of light and go on their respective excursions at different times. For any one species, as a rule, the biting time lasts only about 30 minutes, but when one species leaves off another may follow. It is said that they do not bite in absolute darkness but may bite all through the night in rooms partially lighted. In Brazil, according to the above authority, all species of anopheles bite in the forest during the daytime but they are not abroad in the great numbers observed at night. According to Smith, New Jersey anopheles often bite the inhabitants while sitting on their porches during the afternoon. The same authority states that *A. crucians*, prevalent in New Jersey, is likely to bite from sunrise until 11 A.M. and from 3 P.M. until after dark; in fact, this species may bite at any time of the day when it finds opportunity in some relatively cool location. Some of the Indian anopheles are said to feed greedily even in the daytime. It is evident that the time when this insect is busy varies within wide limits with the species, the temperature, and the amount of light. It appears, however, from the experiences of Sambon and Low that in the Roman Campagna the anopheles of that region are not active in the bright light of the day.

In discussing the biting habits of anopheles on the Canal Zone, Le Prince makes the following statement:

“So far as we can determine not much malaria is actually contracted by laborers while outside on the work; in fact, we have no case on record where a person on the Isthmus has been bitten by an anopheles when the person was exposed to the direct rays of the sun. Although we think very little infection is conveyed during working hours out in the sunlight, we do know that it is a common occurrence for persons to be bitten in the daytime by anopheles when both are inside of buildings. We have noted that a person indoors may be bitten several times in a period as short as ten minutes, and that anopheles while indoors will take blood at any time between daylight and dark, as well as at night.”

Flight.—How far do mosquitoes fly? This is a highly important question. The answers that have been given to it differ widely. They have been determined by the distances between the places where the insects are found and the nearest breeding pools. Since mosquitoes may breed in very small collections of water, such as those formed by the foot-

prints of animals and since these may be easily hidden by vegetation, rubbish, etc., it is not always easy to determine the distance between the place where the insect is found and that where it breeds. Craig states that in the Philippines anopheles may fly two and one-half miles, but Howard is inclined to the opinion that this is an overestimate. However, the correctness of Craig's observation has been conclusively proved by the studies upon the flight of anopheles mosquitoes in the Canal Zone and recorded in the Reports of the Health Department, Panama Canal, for 1919 and 1920. Experiments made with marked anopheline mosquitoes by observers in the Canal Zone, showed that these mosquitoes liberated at distances of over two miles from selected habitations were caught again in the habitations and it was definitely proved that there was a regular daily flight of *Anopheles albimanus* and *Anopheles tarsi-maculata* into the City of Colon from a swamp over two miles distant, one mile of which was across the open water of Manzanilla Bay. This daily flight occurred during the early hours of the evening from the swamp to Colon, the mosquitoes returning to the swamp in the early morning hours. During this time the insects could be observed in countless number crossing the bay and the flight occurred without reference to the prevailing winds and upon absolutely calm days. Pressat, studying conditions at Ismailia in Egypt, came to the conclusion that anopheles are not capable of long, continuous flight. He admits that they are frequently found long distances from their breeding-places, but he thinks that they have come by relatively short stages. Moreover he points out, as all will admit, that they may be transported by boat, wagon, railway, or any other manner by which man may travel. Celli is quite sure that the anopheles present in southern Italy do not fly greater distances than from 300 to 350 meters, and when they are found at greater distances from their breeding-places it must be assumed that they have been carried, at least part of the way. From observations made in China, Young concludes that malarial mosquitoes do not fly more than 200 yards.

Migration in flocks has been reported from time to time, and in one instance at least it was believed that the mosquitoes came from a marsh 35 miles distant. There are stories told about clouds of mosquitoes sufficient to darken the sun and to weigh down the grass and shrubs upon which they alight. An ancient Roman writer tells how mosquitoes in great numbers are useful to man in tropical countries by reducing the number of lions:

"The lions wander in countless droves among the beds of rushes on the banks of the rivers of Mesopotamia and in the jungles, and lie quiet all the winter, which is very mild in that country. But when the warm weather returns, as these regions are exposed to great heat, they are forced out by the vapors, and by the size of the gnats,

with swarms of which every part of that country is filled. And these winged insects attack the eyes, as being both moist and sparkling, sitting on and biting the eyelids; the lions unable to bear the torture are either drowned in the rivers, to which they flee for refuge, or else, by frequent scratchings, tear their eyes out themselves with their claws, and then become mad. And if this did not happen the whole of the East would be overrun with beasts of this kind.”

It is a well-known fact that mosquitoes often visit ships which lie within a half mile of shore; in fact, both malaria and yellow fever have appeared on ships so situated and when there has been no direct communication with the shore. It is not supposed that the mosquitoes fly to such ships with the intention of securing food. It is more probable that they are wandering at random and thus come to the ship. Hosts, not only of insects, but of birds as well, have been known to fly out to sea to their own destruction. The distance from land covered by mosquitoes in reaching the ships is quite definitely stated in all reports of such occurrences with which we are familiar. We know of no instance in which this distance has been reported as more than a mile and generally it is stated at half a mile. However, the greatest care must be exercised in drawing any conclusions concerning the presence of mosquitoes on board ships. In order to be of any value these observations must determine, in the first place, that the ship was free from mosquitoes when it reached its anchorage; in the second place, there must have been no communication by rowboat or tug with the land, since the mosquitoes might have been passively transported in this way; in the third place, it would be well to know that the mosquitoes infesting the ship abound on the land from which they were supposed to come. Roe states that he once found several foreign species of mosquitoes on board a ship at quarantine in New York harbor; indeed, it has been observed that mosquitoes may breed in tin cans containing water and other like receptacles on board ship, and they have frequently been found breeding in bilge water and in wooden barrels. Ross says that mosquitoes may be carried long distances in sailing ships, but that the vibration on steamers prevents their coming to rest and leads to their exhaustion. However this may be, the same author goes on to state, what every traveler can verify, that on warm days many mosquitoes may be seen in railway carriages and that they are not easily dislodged from their resting places even by the jolting of a rough train. It is a common opinion that mosquitoes may be carried long distances by winds; indeed, in studying the location of habitations with reference to marshes even miles away, a special inquiry is made about the prevailing winds, for the reason that mosquitoes are believed to be brought by the wind. Reports are easily found in which it is stated that mosquitoes are brought by the wind through distances of many miles. In most of these, as in cases of flock

migration, careful investigation shows that the mosquitoes come from unrecognized breeding places nearby. Those who have studied mosquitoes and their habits most closely are strongly inclined to the belief that mosquitoes keep out of wind so far as possible. Mosquitoes are disinclined apparently to be swept passively away by a wind, and when they are threatened they seek shelter. During the continuance of a wind men notice that they are not pestered by mosquitoes and conclude that the wind has driven them away; but as soon as the wind dies down the mosquitoes are as abundant and as pestiferous as ever. Indeed, they have not been driven away by the wind, they have simply gone to local shelter. In his study of malaria on the Island of Mauritius, Ross stationed trained "moustiquiers" at different distances from Clairfond Marsh, the chief breeding-place. These men were instructed to catch all the anophelines that came within their reach. On warm, still nights these pickets caught mosquitoes half a mile from the marsh, but on windy nights they caught them only in sheltered spots—behind houses, hedges, etc. It has been suggested that the eggs and larvae of mosquitoes may float long distances down rivers near the banks of which they have been deposited. This is a possibility but not a likely probability. Larvae carried even into a slowly running stream would in all probability be devoured by fish before they had traversed many miles.

Christophers formulates his conclusions after a study of flight distances by mosquitoes in Sierra Leone, as follows:

"(1) In every case where an abundant food supply existed, anophelines traveled long distances (half a mile or more) to reach it, and traversed an equal distance, if necessary, to lay their eggs. Where, however, a suitable breeding-place lay near at hand they did not appear to pass it over. (2) The maximum distance of flight of *A. rossi* is not known with certainty, but under conditions at Mian Mir the experiment showed that they flew to and fro a distance of more than half a mile. (3) The breeding-places of *A. fuliginosus* were in no case nearer than 1,000 yards from the situation where the adults were captured. (4) In the later part of the season it was difficult to understand where adult *A. culicifacies* came from unless distances of half a mile or more were traversed by this species."

It seems safe to state that, as a rule at least, mosquitoes do not proceed by direct flight more than two miles. They may be found at greater distances from the places where they breed, but in most instances they have reached these distances by successive short flights, or by passive carriage.

Ross has gone more fully than any one else into a study of the length of flights by mosquitoes. He says that some mosquitoes, notably the *stegomyia*, may successfully fly against a breeze of five miles per hour, and he roughly estimates the velocity of their flight at about eight miles an hour. At this rate, if a mosquito was to fly continuously in the same direction from its breeding-place, it might traverse a hundred miles or

more during its life. It is not so much a question of what is their power of flight or how far they can fly, but of how far they actually do fly on the average. Ross discusses the random scatter of animals from a given point as follows:

“Suppose that an animal is liberated at a given point—for instance a mosquito from a box—and suppose that it can find its food equally well anywhere in the surrounding country, and is not driven towards any particular spot, or driven anywhere by wind or other things; what are its movements likely to be? We can imagine that it may *just possibly* continue always to move in the same direction, so that when it dies it will be found at the greatest possible distance from the point where it was liberated. Or it may move for half its life in one direction, and for the other half of its life back again—so that it will die actually at the point where it started. But both these courses will scarcely ever be adopted. In the vast majority of cases, the animal will move for a short distance, first in one direction, then at an angle in another direction, then again at another angle, and so on until it dies. Its movements will resemble those of a grain of dust placed on a level plate in a jolting railway carriage; or the random walk of an intoxicated person in a mist; or that of a cow grazing on a uniformly succulent meadow. What are the chances that when the animal dies or ceases to move it will be found at a given distance from the starting point? Obviously, it will most probably be found somewhere near the starting point. There is no reason why it should move more in one direction than in another. The chances are equal that, at any change which it makes in the direction of movement, it will next move north, south, east, or west. Hence its various movements will always tend in the long run to annul each other—so that it will tend to finish near where it began. But there is no *certainty* that its various movements will annul each other *exactly*; hence, most probably, it will not be found exactly at the starting point, but only somewhere near it. * * *. Suppose that a million anophelines are liberated from a single breeding-pool in the midst of a country where they can obtain food equally well at any point, and suppose that we know their average rate of movement and length of life: how many of them will be found at a given moment at a given distance from the pool? Most of them will be found, not exactly at the breeding-pool, but close to it. A few will be found farther away, and a very few at the extreme limit of possible flight.”

At the request of Ross the “law of random scatter” has been worked out mathematically by Pearson and Blakeman. From these calculations Ross draws the following conclusions: (a) Unless mosquitoes are drawn or driven in any particular direction or directions, their number will tend to be greatest somewhere near the breeding-pool, and to diminish progressively at greater distances from it. (b) *Per contra*, if the mosquitoes are very numerous, then, *ceteris paribus*, the breeding-pool is likely to be near at hand.

Ross himself is well aware of the fact that the “law of random scatter” is subject to many variations. In the first place, the food roundabout is not equally distributed and there are food attractions in certain directions. In the second place, there are many, or are likely to be many, breeding-pools and among these there is opportunity for the insect showing some discrimination in the selection of the place where

she deposits her eggs. Lastly, there is the possibility of the "law of random scatter" being put out of gear by passive transportation.

The question of distance of flight in mosquitoes is one of the most important factors in the control and eradication of malaria. No absolute rules, no exact mathematical data, no universally applicable directions, can be made or given. Local conditions must be thoroughly studied. It might be profitable, however, to theoretically consider some of these points. Suppose that there is only one breeding-place in the neighborhood and this cannot be drained, how far away can a man live and be free from the possibility of infection through mosquitoes without taking any special precautions? In a rough way we may say that a mile is sufficient (some would double this), but in the course of this mile there may be a dozen or more houses in which there are cases of malaria and in which the mosquito on its way to *our house* may not only rest, but may feed upon malarial blood. Moreover, the plant life and the animal life between the marsh and *our house* may be factors involved in the problem. Mosquitoes need not fly through this distance of one mile, but they may be carried a part or all of the way on some domestic animal. We are compelled to the conclusion that under the supposed conditions it still will be necessary to screen *our house* and possibly take other precautions. However, while *our house* is likely to be troubled by an occasional mosquito, the chance of being infected with malaria in *our house* is small. We are inclined to the opinion that this chance will be smaller the larger the number of dwellers between the breeding-place and *our house*. The female mosquito in her search for a meal of human blood is driven by the strongest impulses that actuate all living animals, including man and mosquito. In the first place, the female mosquito in her search for human blood is urged on by hunger, the desire to feed herself. But the great factor in directing and continuing her search for blood is even stronger than that of hunger, it is the maternal instinct, the unconscious desire to perpetuate her kind. Having gorged herself with blood, whether it be malarial or nonmalarial in content, the next impulse of the female is to deposit her eggs in the most suitable place within her reach; therefore, she returns to the breeding-place and performs this life function. If it should happen that a mosquito on its way to *our house*, under the supposed conditions, does feed upon a malarial person she will not be able to transmit the disease to the next person she bites, provided she was not already infected, until after a lapse of 10 or 12 days. It is a matter of common observation, and one which is so self-evident that it needs no explanation, that in cities and villages located in highly malarious countries the safest place to avoid infection is at or near the center of the city or village, pro-

vided that breeding-places do not exist within the limits of the city or village.

Following Ross again, but modifying to some extent his suppositions and likewise modifying his arguments, we shall suppose a highly malarious plain with breeding-places of like attractiveness quite uniformly distributed over it. In a theoretical discussion, the size of this plain may vary within wide limits. Suppose that we build in the center of this plain a village, and in our theoretical discussion this also may be small or large. It must be provided that in the building of this village we obliterate all breeding-places covered by it; in other words, the village constitutes a sterilized area in a malarious plain over which the breeding-places were originally uniformly distributed. It must be evident that in this suppositious case we would reduce the number of mosquitoes bred in the whole plain in increasing proportion as the size of the sterilized area approached that of the whole plain. If originally the entire plain produced monthly 100 billion mosquitoes and the sterilized area produced by the building of the village occupied one-tenth of the plain, then the number of mosquitoes produced monthly on the whole plain would be 90 billion. There would be left now 90 billion mosquitoes to infest the territory which had previously been infested by 100 billion. Moreover, under the changed conditions all the mosquitoes are now bred outside the sterilized area. We think there is no need of a mathematical formula to demonstrate that the point of greatest safety from mosquito bites would be at or near the center of the sterilized area. As Ross says:

“The larger the sterile patch the smaller will be the mosquito density due to immigration into it from outside.”

Of course, this reasoning will not hold if breeding-places are allowed to continue within the village. Actually this not only happens sometimes, but the number of breeding-places in the area covered by the village is increased by tin cans, tubs, watering pots, mud holes, and other artificial breeding-places.

Resting Position of Anopheles.—On this point, Howard makes the following statement:

“Much has been said concerning the resting position of anopheles as compared with that of other mosquitoes. It has been held that anopheles always sits with its body-axis at a considerable angle to the surface upon which it rests. This, however, cannot be relied upon for identification. When anopheles rests upon the surface, such as the wall of a room, the body is frequently held at only a comparatively small angle to the surface; in fact, it is sometimes held parallel but more often at a considerable angle. The angle at which the body is held differs with the species and is characteristic for it. The hind legs are frequently in motion but as a rule hang down with more or less of a bend at the knee joint. In whatever position anopheles rests, the beak and the rest of

the body are practically in the same plane, whereas with other mosquitoes the beak and the abdomen are by no means in the same plane.”

Craig gives the following testimony:

“The resting position of adult anophelines and the position assumed when biting, the two being practically identical, offers one of the easiest and most valuable methods of differentiating between them and other mosquitoes. When resting upon a flat surface, as a wall, the mosquitoes belonging to the anophelinae, with few exceptions, form a distinct angle with the surface, the insect resting upon the first two pairs of legs, the last pair floating in the air or held out straight behind it. The angle formed by the body of the mosquito and the surface varies, but sometimes is nearly a right angle. The only exceptions to this rule among the anophelinae commonly observed are *A. culicifacies*, *A. superpietius*, and *A. hispaniola*, which assume a perpendicular position in reference to the wall. The position assumed by other mosquitoes, as *Culex*, *Stegomyia*, etc., is well described as ‘humpbacked,’ the abdomen approaching the resting surface while the thorax is distinctly higher than any other portion of the body, thus giving the humped appearance. Whatever the position of a mosquito it can always be determined whether it is an anopheline by attention to the relative position of the proboscis to the body. In the anophelinae the proboscis is always in a direct line with the rest of the body when the insect is resting upon a surface, while in all other mosquitoes the proboscis forms an angle with the abdomen. This peculiarity is easily recognized and gives the anopheline a distinctly business-like appearance, the entire body of the insect resembling a boring instrument.”

Feeding Habits.—As is well known, the male anopheles cannot pierce the skin of man and does not feed upon blood. He draws his daily ration from plants mostly, though possibly he may feed to some extent upon other insects and upon dumb animals; but so far as observations go the evidence points to the probability that he is a strict vegetarian. On the other hand, the females of certain species of anopheles, those which serve as malaria carriers, apparently depend upon man for their food. According to Jennings, *A. eiseni* is abundant in the jungles of Panama which are seldom or never visited by man. This species does not transmit malaria. On the other hand, *A. albimanus*, which is the chief malarial distributor in the American Tropics, is found only in localities inhabited by man. It is reasonable to infer that mosquitoes which do not feed upon man procure their blood from animals. Schüffner found in Sumatra one species of anopheles that could not be induced to feed upon man, while in the same localities or nearby places he found another species most greedy for human blood. He found that when numbers of the latter species were captured, placed in a cage and allowed to starve for a while, they seized upon the human hand introduced into the cage, began to sting immediately, and did not easily permit themselves to be disturbed. One could touch or even shake them without inducing them to withdraw the proboscis. He found the voracity of these mosquitoes incredible. He writes as follows:

“The ordinary *culex*, after it has sucked its fill, flies away. These anopheles, however, are not satisfied with this but continue to suck, making more room by discharging the surplus through the anus. At first they discharge the feces and intestinal liquid, but afterwards, drop by drop, pure blood follows. So, before it chooses to fly away it flushes its digestive tract with three to four times the amount of blood which would have been necessary to fill its stomach.”

Grassi has made a careful study of the feeding habits of anopheles in Italy. He concludes that the normal food of anopheles is blood, preferably the blood of mammals, not necessarily the blood of man. Grassi's observations led him to conclude that, so far as the Italian anopheles are concerned, the predilection for a particular mammal is determined by the size of the animal rather than by the species. When man and horse are simultaneously exposed the horse is bitten many times before the mosquitoes fasten on the man; indeed, horses are said to attract mosquitoes. Upon this animal they will locate themselves more numerous and in these positions are easily captured. On the other hand, if the mosquito has a choice between man and dog or man and rabbit it prefers man. The Italian anopheles comes on to porches and into houses in the early evening twilight, and having gorged itself with blood, seeks a hiding place where it can enjoy its siesta and digest its food. During the daytime it remains quiescent, generally finding a resting place on the underside of leaves and selecting spots where it is best protected from sun, wind, and rain. Naturally, it does not go far from its feeding place and when hungry returns to the same locality. At least in some countries, and this seems to be true of widely separated localities, anopheles are particularly fond of stables. This predilection for stables has been observed and remarked upon by Grassi in Italy, by Kinoshita in Japan, and by Mühlens in northern Germany. The last-mentioned observer, reporting on his observations in the vicinity of Wilhelmshaven, found large numbers of anopheles in the warm stables occupied by cattle and hogs. The stomach contents of these insects were tested by the specific agglutination method and found to contain the blood of cattle or hogs according to the animal with which the individuals examined were found to be associated. Grassi thinks that anopheles are attracted to stables by the size and number of animals and by the warm temperature. Anopheles often hibernate in stables.

Anopheles are ready to suck blood within from 24 to 48 hours after emerging from the pupa. This is true in tropical countries, but in cooler regions a longer time is required before the young mosquito acquires strength enough to develop its predatory habits. Grassi found that the Italian anopheles will feed daily, even when they have not fully digested the last meal. Neiva, studying the Brazilian species, finds that the biting activity of anopheles is influenced markedly by weather con-

ditions. He notes that when rain is threatened, anopheles become very numerous and blood thirsty. This observation will find ready acceptance by all who have lived in mosquito ridden countries. According to our own observation on this point, the mosquito manifests its greatest activity in the calm that precedes the storm. We have been inclined to attribute this well-known fact to several factors. In the first place, there is increasing darkness; in the second place, elevation of temperature; and in the third place, the air is at rest. All these conditions favor the activity of this pestiferous insect.

According to Grassi, the female anopheles will join her mate in sucking the juices of fruits and plants when she cannot obtain blood. One is inclined to the suspicion that the voracity of the female for blood is in some way connected with her fecundity; although Craig states that a meal of blood is not essential to either the laying or the development of the eggs.

Hibernation.—According to Giles, there are many localities in India in which anopheles may be found in all stages every month in the year, decreasing in numbers in the hot season and increasing during the rains. In tropical countries the activity of the mosquito is influenced largely by conditions of moisture, and it is during the dry season that this insect is least in evidence. In colder regions the species is kept in existence during the winter solely by the fecundated female. According to Smith, in New Jersey the female begins to seek winter quarters in September. Preparatory to her long-continued fast she stores in her abdomen a mass of fat and upon this she sustains her feebly exercised life functions during the winter. She retires to some cellar or attic; or attaches herself to the underside of a shelf in the pantry, where Hodge found mosquitoes in Worchester, Mass., literally by the thousands. Resting in such secluded places the fat stored in her abdomen is sufficient to supply her scanty wants, and when spring or summer comes she is ready to deposit her eggs in the most suitable nearby breeding-place that she can find. Even in the northern United States, the high temperatures reached in many dwellings during the winter time leads to unusual activity on the part of the hidden guest. She comes from her hiding place, becomes active, and has been known to bite even in midwinter. It is evident from this that the behavior of the mosquito during hibernation is controlled largely by temperature and moisture. Attention has been called to the desirability of the fumigation of cellars, closets, and stables during the winter in malarious countries.

Domesticity.—*Culex pipiens* and *Stegomyia calopus* are known as domestic mosquitoes. They breed in and about houses and apparently they prefer to remain in the localities where they breed or thereabouts.

The malaria bearing anopheles are generally regarded as semi-domestic species, while those which do not transmit malaria are classed as wild species. On this point we make the following quotation from James and Liston, concerning the domesticity of several species of anopheles in India:

“It is a well-recognized fact that some species of anopheles are more commonly found near villages and dwellings than others. We may, in fact, divide these insects broadly into two classes; the domestic species, which are usually found near human dwellings, and the wild species, which are rarely found in houses. Of the first class, *A. rossi* is a typical example, and of the second, *A. barbirostris*. Some species would appear, as regards this habit, to occupy a place intermediate between the typically domestic and the typically wild species. *A. fuliginosus*, for example, may, in certain parts of India, be found in enormous numbers in the sheds and outhouses on the outskirts of a village, while in other parts, though large numbers may be caught in tents pitched at some distance from a village, few or none will be found in the houses of the village itself. It is usual to say that the greater the number of anopheles there are in a place, the greater will be the prevalence of malaria. This is not by any means borne out by experience. We have already mentioned that some species of anopheles are better malaria carriers than others, and apart altogether from the fact that anopheles may be abundant in a place without there being any malaria there at all, it often happens that the species which is present most abundantly is not the one which is carrying malaria at the time. It is, however, a difficult matter to estimate the relation between abundance of different species in any place, for some are much more easily seen than others, and the habits which some species have of secreting themselves among the straw of a thatched roof and of resting only on objects which are as nearly as possible the same color as they are themselves, are very important. In order to exemplify this, it seems worth while to recall an instance which happened in our experience. In the malarious village of Ennur in the Madras Presidency, *A. rossi* was so abundant that on almost every straw of the thatched roof of every house three or four specimens of this species were resting. A careful search in the ordinary way did not reveal the presence of any other species, and it is certain that had there been no other object in the search than the mere determination of the species of anopheles present in the village, the observer would have gone away quite satisfied that *A. rossi* was alone present. But the village was an extremely malarious one, and knowing that *A. rossi* are inefficient carriers of malaria in nature, he was unwilling to believe that no other species was present in the house. Fixing his mind, therefore, upon the thought that he was looking for *A. culicifacies* and not for *A. rossi*, he again commenced the search with great care and was rewarded not only by detecting the presence of *A. culicifacies*, but by catching a sufficient number of this species during several days' work, to prove that it was the species responsible for the presence of malaria in the place, and not the very much more abundant species *A. rossi*.”

Color Attraction.—It is well known to all who have visited mosquito infected countries that the mosquito prefers dark to light colors and that individuals dressed in black are more readily and repeatedly attacked than those who dress in white. Austen states that if the walls of a room be whitewashed, with a dark dado, insects lighting on the walls will always be found on the dark strips. As we shall see later, this has been used in reducing the number of mosquitoes and in eradi-

eating malaria. According to Buchanan, the natives of India recognize the preference of mosquitoes for black and they hang a black coat in the room or in a hospital ward when they desire to catch anopheles. Joly, making his observations in Madagascar but without stating the kind of mosquitoes he was dealing with, says that it is well known that these insects prefer a red or black soil to one of white sand, and, moreover, that persons wearing black shoes and socks are more frequently bitten than when these articles are white. According to the same authority, brown affords less protection than white or black. This authority states that the natives of Madagascar well know the attraction of black to mosquitoes and for this reason they hang an article of black cloth on the rafters in order to protect the inmates. The native blacks are bitten more frequently than the whites, and this color attraction seems to hold good for the lower animals as well. Nuttall and Shipley made experiments in color attraction using *A. maculipennis*. They placed in a large gauze tent boxes of different colors. In the same tent was a basin in which the anopheles were bred. Their report is as follows:

“It was noticed at the beginning that when one entered the tent in dark grey clothes that the imagos frequently flew up and settled on the dark cloth, but that they never did this when the person entering the tent was clothed in white flannels. To test the influence of color, a number of paste board boxes were taken which measured 20 by 16 cm. and had a depth of 10 cm. The boxes were lined with cloth, having a slightly roughened surface to which the insects could comfortably cling. All of the fabrics had a dull—not shiny—surface, and each box was lined with cloth of different color. The boxes were placed in rows upon the floor and upon each other in tiers, the order being changed each day after the observations had been made. The interior of the boxes

TABLE XXVIII

COLOR OF BOX	NUMBER OF <i>A. MACULIPENNIS</i> COUNTED IN EACH BOX DURING 17 DAYS
Navy blue	108
Dark red	90
Brown (reddish)	81
Scarlet	59
Black	49
Slate grey	31
Dark green (olive)	24
Violet	18
Leaf green	17
Blue	14
Pearl grey	9
Pale green	4
Light blue (forget-me-not)	3
Ochre	2
White	2
Orange	1
Yellow	0
	512

was moderately illuminated by light reflected from the surface of the white tent. On 17 days during a month beginning with the middle of June, we counted the number of flies which had accumulated in the boxes. Counts were actually made on 17 sunny and cloudy days, with the results shown in Table XXVIII.

"We see from Table XXVIII that dark blue was most attractive, the other colors being less and less attractive in the order of number given. A marked fall in the number of insects resting in the boxes begins with the pearl grey box. Pale green, light blue, ochre, orange, and yellow, especially the last two colors, seemed to repel the insects. The khaki-colored uniform now so generally used should offer advantages besides invisibility to human foes."

Jordan and Hefferan made similar experiments with the results shown in Table XXIX.

TABLE XXIX

COLOR	NUMBER OF MOSQUITOES
Dark red	61
Dark blue	57
Black	41
Dark pink	8
Dark green	6
Lavender	5
Purple	5
White	4
Light blue	2
Pale green	2
Light pink	1
Yellow	0

Breeding-Places.—It was once thought that anopheles breed only in still fresh water, but further observation has shown that this conclusion is not altogether warranted and that certain exceptions and modifications must be made for different species of anopheles. Again, it was once supposed that anopheles do not breed in barrels, tin cans, and small puddles around houses and barns. It is true that the culex breeds more abundantly in such places, but the larva of the anopheles was sometimes found mixed in such receptacles with that of culex. Both the culex and the anopheles may be found breeding in roadside puddles and ditches, in water-logged boats, in stone troughs, in small accumulations of water between rows of corn, etc. In Sierra Leone, Austen states that anopheles larvae mixed with those of culex were found in a tub of water in the yard of the sanitary office. Anopheles are often found in dirty water and in that covered with green scum. In Italy, according to Grassi, they are most frequently found in clear water rich in vegetable food. In Free-town, Austen found anopheles larvae in stagnant puddles along the street. It seemed to make no difference whether the water was clear or turbid, whether green algae were present or not, and in some of these puddles tadpoles were numerous. In New Orleans, Veazie found anopheles larvae

in the ponds and swamps just outside the city. In the Havana campaign, Gorgas did his most effective work along small streams which irrigated gardens and similar places. In some cases anopheles seem to have a special preference for pools and puddles well protected with grass. Smith, in New Jersey, says that anopheles breed everywhere. He found their larvae in pails in his backyard, and states that he found no pool so insignificant and no stream so rapid but that somewhere in it anopheles can breed. He says:

"Small creeks through meadow land, the ditches and gutters or drains along railroad and other embankments, and the shallow overgrown edges of ponds or swamp areas are favorite breeding-places. Pools containing grassy or other vegetation are nearly always infested, and ponds with lily pads, dock, sagittaria and other plants of a similar character, are danger points. The larvae need only a mere film of water, and this being found over a leaf or at a grassy edge, protects them from the usual natural enemies. * * *. No other mosquito has as wide a range of breeding-places as have the species of anopheles."

James and Liston, studying anopheles in India, state that in the search for these insects every collection of water should be examined. These observers believe, and in this they are confirmed by many others, that each species has its favorite breeding-ground. In Central America and in Brazil anopheles often breed in water collected in tree holes. These may be far from human habitation. Some species have been found in tree holes many feet above the ground. In the tropics the small accumulations of rain water that appear at the bases of the leaves of certain plants furnish adequate breeding-places for the anopheles of that region. In Brazil, some of these plants are parasitic and grow upon forest trees 30 feet above the ground. In these Lutz found the larvae of *A. cruzii*. According to this author, this species is a typically forest insect, and he thinks it responsible for some outbreaks of malaria which have occurred in Brazil among those engaged in railroad construction. Studying the breeding-places in western Michigan, Jordan and Hefferan came to the conclusion that *A. maculipennis* and *A. punctipennis* select different breeding-places. The former were not found in spring-fed pools, while the latter seemed to prefer these places. On the other hand, *A. maculipennis* were found frequently in the river, while *A. punctipennis* were seldom found in the stream. Craig says:

"In the Philippines a favorite breeding-place of anopheles was the cavity left after cutting off bamboo poles near a joint. In the latter part of the rainy season I have found larvae in nearly every bamboo pole examined, and at Camp Stotsenburg, where temporary quarters for a large number of troops were built of this material, anopheles became a veritable scourge and malaria increased to such an extent that it was found necessary to remove the larger part of a brigade which had been stationed there. Among the breeding-places of anopheles which are most likely to be overlooked may be mentioned the small depressions in the ground produced by the hoofs of animals or the inequalities left in plowed lands."

According to Smith, anopheles breed in the brackish marshes in New Jersey. Vogel, studying anopheles in Java and other parts of the East Indies, comes to the following conclusion:

“(1) There are species of anopheles which can live very well in sea water. (2) These mosquitoes lay eggs which develop even in sea water which has been evaporated to half its original quantity. (3) These larvae in the gradually evaporating pools of water can stand evaporation of the water to one-third its bulk, but do not appear to transform to adults if the concentration be greater than this. (4) The larvae coming from eggs laid in sea water of high concentration can accomplish their entire metamorphoses in almost normal time. This is true even when the water has such concentration that the development of larvae originally hatching in unconcentrated sea water would be retarded by this salt water.”

The reports made by Vogel were for a time questioned, but have received apparent confirmation by Caruthers, making observations on the Andaman Islands and by Lukis in India. The former observed that the prevalence of malaria in certain villages was determined by their proximity to the sea. Those near the sea were invariably malarious, while those more remote were healthy. Even a distance of half a mile from the sea was sufficient to insure freedom from this disease. The evidence so far seems to indicate that, while some species breed only in fresh water, others may breed in either fresh or brackish water, while still others breed only in brackish water. *A. ludlowi* is a malaria bearing mosquito found in the Philippines. Banks has studied this mosquito and at first came to the conclusion that it was never found breeding in fresh water, but later and more extended observation convinced this author that *A. ludlowi* may and does breed quite indifferently in fresh and salt water.

Dutton, in Gambia, made some experiments for the purpose of determining whether anopheles may breed in salt water. He took a garden tub and filled it with tide water. Four days after, a batch of anopheles larvae was discovered in this water, and these subsequently hatched into adult mosquitoes. The species with which Dutton worked was *A. costalis*. According to Howard, several species of anopheles have been found to breed in brackish water in America, but none of them extensively so. Chapin found anopheles larvae living in brackish water on the coast of Rhode Island, and we have already called attention to Smith's observation in New Jersey. In Central America *A. albimanus* breeds both in fresh water and in that strongly brackish. The same is perhaps true of other species of anopheles in the same region.

The resistance of the eggs and larvae of malarial mosquitoes on desiccation is a matter of considerable importance. Evidently, the eggs may be deposited upon damp mud and when this happens if water finds access to the place within 48 hours, as the result of a shower or any other cause, these eggs may hatch and the larvae develop.

Watson, after long experience in fighting malaria in the Federated Malay States, says:

“It has long been established that mosquitoes, including the anophelines, exercise discrimination in the selection of water in which their larval stage is passed. Each species prefers its own special type or character and quality of water as a breeding-place. Some have a wide range, others are peculiarly selective. *A. maculatus* is one of the latter. In Malaya it is found exclusively in hill streams, and in the springs which feed these. I consider that the eggs are laid in, and that the larvae prefer, the shallowest waters; indeed, they are most numerous in ground with so little water on it that, in order to take the larvae, it is often necessary to make an excavation in the earth into which the water from the surrounding ground flows, carrying the larvae with it. As these springs are very common at the head of a ravine, the presence of this mosquito in them probably accounts for the well-recognized danger of living at the head of a ravine. The old explanation for this was that mists were carried up the ravine, and naturally struck with special force those living at its head.”

The same author, describing his experience in searching for mosquitoes in a certain part of Malaya, states:

“But when we came to work out the anophelines, it was found that different species were found in the middle of the swamp from those on the hills. Nature has, therefore, carried out a great experiment. There were three groups of anophelines: One on the hills, one in the rice fields close to the hills, and a third lot in Krian far from the hills. Now, why do these vary? Clearly on account of something in the water, and it can easily be imagined that only a small change would bring the Bukit Gantang water to that of the Krian rice fields, and then malaria would disappear from Bukit Gantang too. I believe that in this way a great antimalaria method will be evolved, and I can look to the time when we will be able to play with species of anophelines, say to some ‘go,’ and to others ‘come,’ and abolish malaria with great ease, perhaps, at hardly any expense. Drainage schemes may become methods of the past, and future generations may smile to think of how their ancestors, who thought they were so clever, burned the house to cook the pig.”

Breeding.—The female mosquito deposits her eggs on the surface of water or upon wet ground. The eggs are not deposited *en masse* as is the case with the culex. Each egg lies upon its side, is single, but 40 to 100 are usually found floating close to one another. The distinguishing mark of the egg of the anopheles is the so-called “float” consisting of an envelope-like expansion along the middle of the egg. Craig says:

“These lateral floats are variously marked in the eggs of different species and vary in size, but are always easily distinguished and of the greatest service in differentiating the anopheles egg from that of other mosquitoes. The eggs are oval in shape and hatch, in most species, in from one to two days, but this varies so much with external conditions and with different species that a general statement is hardly justified. From 30 to over 100 eggs may be deposited by a single female. The eggs will remain alive in moist mud for considerable periods of time, even as long as six days, but cannot resist complete drying for over 12 hours, so far as is known. This fact is important, as it indicates that drainage of pools or other small

collections of water will not be efficient if the mud remains moist until water again gains access to the pool."

The larvae of the anopheles are also easily distinguished from those of other mosquitoes. They remain near the surface of the water and horizontal to the surface. As a rule, the head protrudes from the surface. Other mosquitoes are furnished with a respiratory tube, the end of which lies even with or slightly above the surface of the water, while the body of the larva dips obliquely into the water. The larvae are grey or brownish in color. They undergo four moltings before reaching the pupal stage, and this requires under average conditions from 10 to 14 days, although this time may be reduced by two or three days and may be extended by as many weeks, depending upon environmental conditions. Moreover, development varies somewhat with the species. Howard gives the following description of the larvae and their methods of feeding:

"The larva's head rotates upon its neck in a most extraordinary way, so that the larva can turn it completely around with the utmost ease; it feeds habitually with the under side of the head towards the surface of the water, whereas the upper side of the body is towards the surface. In this customary feeding position, the mouth-parts are worked violently; the long fringes of the mouth-parts cause a constant current towards the mouth and the particles floating on the surface of the water in the neighborhood thus gradually converge to the mouth-opening and enter the alimentary canal. The spores of algae, bits of dust, minute sticks, bits of cast larval skins, everything in fact which floats, follow this course, and, watching the larvae under the microscope, they can plainly be seen to pass through the head into the thorax until they are obscured by the opaque color of the larva's back. This is the common method of feeding when full grown; however, the larva will descend in the shallow water and mouth over the slime of pebbles at the bottom. Occasionally a fragment, too large to be swallowed with ease, clogs the mouth. Sometimes it enters the mouth and sticks. In such cases the head of the larva revolves with lightning-like rapidity until the top of the head is upwards and the fragment is nearly always disgorged, although sometimes it is swallowed with an evident effort. As indicated, the larva feeds upon everything that floats. It is especially often found in stagnant water on which there is more or less of an algal scum; therefore, a very frequent food consists of algal spores, and the color of the larva is influenced more or less by the character of the food, green algae making it green. Daniels, in his African investigations found that the contents of the intestines of the larvae are mainly vegetable matter, in some cases entirely so. 'Occasionally limbs of minute insects or crustaceans are found, as well as scales of mosquitoes or other insects. On watching them feeding, it is seen that minute particles are drawn to the mouth, but many of them are rejected. This rejection is somewhat arbitrary, as a particle at first rejected is often subsequently swallowed. Amongst the bits seen to be swallowed I have seen living minute crustaceans and young larvae, both of anopheles and culices, but as a rule, living animal bodies either escape or are rejected.' Christophers and Stephens state, in their observations in Sierra Leone, the food of the anopheles larvae seems to be a unicellular organism. James and Liston state that the food of anopheles larvae consists chiefly of minute water animals which abound among algae and other water plants. They believe that the larvae cannot subsist upon vegetable diet alone and that the duration of the larval

stage depends chiefly upon the supply of animal food. When this is small in proportion to the number of larvae, they starve, the stronger larvae kill and eat the weaker."

From observations made in Switzerland, it seems that the larvae of *A. bifurcatus* normally hibernate, remaining among the leaves of watercresses and other aquatic plants. They have been found in thin layers of water between two sheets of ice.

The pupal stage of mosquitoes is passed in the water and is the shortest period in the life of the insect. In duration it varies with the species and with external conditions. The pupae of the anopheles differ in no essential way from those of other mosquitoes. When the pupa reaches maturity it rises to the surface of the water, the skin over the thorax breaks open, and the adult mosquito is liberated.

Number of Generations.—It is commonly believed that during a single season there are many generations of anopheles, each of which begins to reproduce its kind shortly after the evolution of the imago. It appears that the only scientific observations bearing on this point have been made by a Russian, Kulagin, who came to the conclusion that there is only one generation of mosquitoes each year; in other words, those developed during one summer do not begin to lay eggs and reproduce their kind until the next season. On this point, Howard makes the following statement:

"Further observations are necessary to determine if all the species of anopheles of the temperate regions agree in the number of generations. As to the tropical species, practically nothing is known as to the number of generations. Quite probably in certain regions, where there is an abundance of water throughout the year, breeding is continuous. In parts of India, where there is a long, well marked dry season, the behavior of the anopheles appears to be much as in colder climates, only that in these countries the dry time is the resting period. Stephens and Christophers state that in India estivating anopheles, although they feed at intervals, will not deposit eggs even if suitable deposits of water are present."

Mosquito Enemies.—Fortunately, the mosquito has many natural enemies. If it were not for this the number of these pestiferous insects would probably become so great that man would have difficulty in withstanding their attacks. There are certain fungi which undoubtedly destroy large proportions of the mosquitoes breeding in these regions. The following report by Pettit, of the Michigan Agricultural Experiment Station, is of interest in this connection:

"On August 5, Mr. Barlow found a number of adult mosquitoes killed by a fungus, *Entomophthora* sp. nov. They were very numerous on the margins of one of the pools in the north woods, sometimes almost covering the soil and the pieces of bark to which they clung. Some were just killed and showed little, if any, external growth; and some were covered with a dense dull white growth. All were within a few inches of the water and all faced away from it. Imagine thousands of mosquitoes all headed away from the water as if they were trying to get away from it. It would seem that the effect of the disease is to draw the affected insects to the water, pos-

sibly by creating a thirst, after slaking which, the insects, in trying to retreat, are caught and stopped in their course by numerous rhizoids or anchor ropes which are sent out by the fungus in the body to fasten the victim permanently to the place where its ill-luck overtakes it. Unfortunately for the mosquito host the diseased individuals die just in the right place to infect their fellows as they come to the pool to drink or to lay eggs. This is a case where the fungus seems to influence the host in such a way as to lead to the spread of the disease. Similar impulses seem to be induced in the case of other species—the *Sporotrichum* that is used against chinch-bugs seems to impel the diseased individuals to hide under clods or any other moist and protected places, just the places where the young bugs come to shed their skins or to molt. This is, of course, the best possible way to spread the disease. Then, too, in the case of the common grasshopper disease, *Empusa grylli*, the dying hoppers are impelled to climb to the tops of weeds and plants and as the fungus throws its spores to some distance, there is a good chance that some of them will fall on the bodies of other grasshoppers. The appearance of the mosquito fungus is quite characteristic. The entire body is swollen and covered with a dull white growth, sometimes almost plumbeous. The body is fastened down by many slender brownish ropes. A microscopic examination shows the growth to be of fine threads (mycelium) bearing spores at their distal extremities. These threads are usually simple, though sometimes bearing a few short branches. They are septate at long intervals, granular and contain vacuoles. The spores are lunated and bluntly rounded at both ends. In size they measure about 50 microns long by 13 in diameter, some being as long as 55 microns and a few as short as 28. They are finely granular with oil globules usually near the end. In a single specimen large numbers of resting spores were found.”

Among the anopheles in Italy, Perroncito found a bacterial parasite. This infests the larvae and destroys the mosquitoes soon after they reach adult life. There is also a yeast which is pathogenic to the mosquito. It was thought by Schaudinn that some of the yeasts found in the stomachs of mosquitoes are physiologic and are of benefit to the mosquito. A spirochete has been found both in the larva and in the adult anopheles, and Gregarinae are abundant parasites in mosquitoes and other insects. Just what harm these parasites do the mosquito and how greatly they aid in reducing the number of these insects we cannot tell.

The fresh-water hydras eat great numbers of the larvae of mosquitoes. A minute trematode has been found encysted in anopheles. It is believed that bats become infected with a trematode from eating mosquitoes. According to Stiles, these parasites are decidedly injurious to mosquitoes. The infected insects were observed to be very sluggish in their movements and could easily be recognized as diseased. Many of them died from the effects of the parasite, and the ovaries of infected females were undeveloped. Smith, studying mosquitoes in New York, is confident that a ring-worm parasite constitutes a very material check to the multiplication of certain species of mosquitoes. However, the presence of this parasite does not prevent the flying or interfere with the biting qualities of the infested insect.

There are many carnivorous insects which feed upon mosquitoes that are seldom or never found in artificial receptacles and in temporary pools. Howard took a half gallon of water from a stagnant pool which was teeming with aquatic insects, including hundreds of mosquito larvae. Among these insects were three larval hydrophilid and in the course of a week these devoured practically all other animal life in the jar. Smith is of the opinion that the larvae of the Dytiscidae are among the greatest enemies of mosquitoes and he is inclined to attribute the comparative freedom of a hilly section of New Jersey largely to these insects. According to Viereck, one good-sized dytiscid larva devoured 434 mosquito larvae in two days. According to Smith, the so-called "whirligig beetles" are great destroyers of mosquito larvae and he states that no anopheles larva has a chance in any bit of water inhabited by these beetles. The same authority accredits good work in the destruction of mosquitoes to certain aquatic bugs. It is so well known that dragon flies feed upon mosquitoes that attempts have been made to multiply the former in areas where the latter have been greatly and painfully in evidence. Although a volume has been written on "Dragon Flies vs. Mosquitoes," nothing practical has come out of this attempt. Howard says:

"We are of the opinion that dragon flies do destroy a great many mosquitoes. While they show no preference for mosquitoes there seems to be, on the part of the adult dragon flies, a marked preference for Diptera; with their great rapidity and activity, where mosquitoes are abundant, a considerable number must be destroyed by the dragon flies."

Among the mosquitoes themselves there are many cannibals, but in all the references at our command it seems that anopheles larvae devour eulex larvae. Undoubtedly there are among insects many species which feed upon and decimate mosquitoes, but to try to drive out one insect by improving the living conditions of another may turn out to be like driving out the devil with Beelzebub.

Certain ascarids or mites are frequently found attached to the bodies of adult mosquitoes. Thibault, studying mosquitoes in Arkansas, says that more or less every adult specimen of certain species is found to be infested by a red mite very similar in general appearance to those occasionally found on house-flies, though for the most part such will be the case only early in the season. The proportion of infested individuals among the various species is very striking, anopheles and mansonia showing the greatest number of infested individuals; likewise the greatest number of mites per mosquito.

It is well known that spiders entrap and eat mosquitoes. McCook counted in an orb weaver's snare, spun upon the railing of the long bridge over Deal Lake, N. J., 38 mosquitoes at one time hanging en-

tangled upon the viscid spirals. The same authority recommends that the multiplication of spiders be favored in order to decrease the number of mosquitoes. In Brazil the jumping spiders seem to be an effective check upon mosquitoes in houses. The commission sent from the Pasteur Institute to study yellow fever at Rio de Janeiro found that their studies were seriously interfered with by spiders which destroyed the mosquitoes they were desirous of studying. Smith seems quite confident that the number of mosquitoes destroyed by spiders in New Jersey is large and he thinks that many spiders subsist largely upon mosquitoes. Leon, studying in Roumania, finds that enormous numbers of mosquitoes are caught and killed by the spiders which weave their webs on sedges, reeds, and willows growing about swamps.

Frogs and toads have a reputation for destroying mosquitoes. Some frogs apparently feed largely upon mosquito larvae, while most frogs and toads eat adult mosquitoes. It has been stated that tadpoles destroy mosquito larvae, but this is probably not true, since tadpoles are strict vegetarians. They may disturb the hatching of the eggs and the development of the larvae by causing violent movements in the water on which the eggs are deposited.

According to Giles, there is a little lizard common in the bungalows in India which is quite efficient in destroying mosquitoes. This lizard is known locally by the name "gecko," and Giles states that one gecko is quite equivalent to a fly-paper of the largest size in destroying mosquitoes.

There are insectivorous birds which feed on the wing and devour mosquitoes in great numbers. Among the birds known to feed in this way on these insects are night hawks, whip-poor-wills, chimney swallows, and the tyrant fly catchers. Enormous numbers of the larvae of mosquitoes are eaten by aquatic birds, notably ducks, and there are nine species of shore birds, such as the sandpiper, that help in materially decreasing the number of mosquitoes arising from breeding swamps.

It is well known that bats play an important rôle in certain countries in the destruction of these pests. It has been seriously proposed that bat-breeding houses be provided near swamps from which mosquitoes arise. Certain insectivorous plants, notably the bladderworts of the genus *Utricularia*, trap and destroy many insects, including probably all species of mosquitoes. In some countries it is probable that these plants exercise a certain degree of mosquito control.

The Employment of Fish in the Destruction of Mosquitoes.—It has long been known that certain fishes feed voraciously upon mosquito eggs and larvae, but it is only within recent years that fish have been employed scientifically in the eradication of these insect pests. It is a

matter of record that mosquitoes are not abundant in Barbados as compared to other West Indian Islands. It is a common practice among the natives to keep small fish in their drinking-water barrels and at the same time fish abound in the natural waters on the Island. Boyce states that when the native residents are asked why they keep fish in their water barrels they say that they have been taught to do so by their parents or grandparents for the reason that if a maliciously inclined neighbor should poison the water the fish would die, float on the surface, and thus indicate that the water is dangerous.

In recent years much attention and considerable scientific study have been devoted to the selection of fish best suited for the destruction of mosquitoes. The fish in Barbados are known by the popular name of "millions." The female when full grown is dull in color, without conspicuous markings, and measures about an inch and a half in length. The male is much smaller but carries irregular red dots and has a circular dark spot on each side. This fish thrives in captivity and seems to be quite at home in tanks, reservoirs, garden tubs, fountains, etc. They are hardy little animals and bear transportation even when not carefully attended. They have been distributed from Barbados to many other West Indian Islands and apparently have proved of marked value. Of course, it will be understood that the success of the transplantation of any form of either vegetable or animal life will depend upon many circumstances. There are several genera of small fish found in the stagnant waters at sea level along the coast of the Gulf of Mexico, especially in Texas. One of the most abundant of these is *Gambusia affinis*. This species is widely disseminated in tropical and subtropical countries. It has been carried from Texas to the Hawaiian Islands and has there been used successfully, it appears, in the warfare against mosquitoes.

It is worthy of remark at this place that the presence, breeding, and abundance of "millions" on the Island of Barbados are not regarded by experts who have studied the local situation, as a satisfactory explanation of the absence of anopheles on the Island. *Culex* and *Stegomyia* are abundant. Filariasis is not uncommon, and, indeed, the Island is acquiring an undesirable reputation from the phrase "Barbados leg," which is becoming apparently more and more applicable to that locality. In 1908 there was on this Island an outbreak of disease which was reported as yellow fever. Guiteras thinks that it possibly might have been febrile jaundice. However this may be, *stegomyia* are common on the Island. Balfour has discovered in the waters of the Island, in addition to the "millions" a little back-swimmer of the genus *Notonecta*, and he has observed this animal feeding upon the larva of the *stegomyia*. According to Sambon, the rugged

northern part of the Island furnishes a natural oil which floats on the surface of the streams and prevents the development of not only mosquitoes, but of all aquatic life. Low has shown that there is nothing in the chemical constituent of the waters of Hastings Swamp on the Island which is inimical to mosquito life. Balfour thinks it strange, admitting that there are no suitable breeding-places for anophelines on the Island, that this mosquito is not imported on some of the numerous small craft which visit the Island frequently from relatively nearby ports where it is abundant. It seems that *Culex* and *Stegomyia* are often found on these boats when they reach Bridgetown, but the anophelines seem to be less expert sailors and, although they, with the *Culex* and *Stegomyia*, are swarming on the boats when they leave British Guiana, Bridger, health officer of the port of Bridgetown, has never found them on the boat when it reaches Barbados.

Gold fish and silver fish thrive in small collections of water, demand but little care, and delight in consuming mosquito larvae. These fish have been employed for this purpose in New England.

The widely disseminated stickleback and the common sunfish or pumpkinseed abound in certain localities and when opportunity is present apparently prefer mosquito eggs and larvae to other delicacies. We have elsewhere spoken of the Brazilian fish, "*barrigudo*," and its employment in Rio de Janeiro in the campaign for the eradication of yellow fever. Certain conditions are necessary in order that fish be of value as mosquito exterminators. In the first place, they must be protected from their enemies. The small fish which feed upon mosquito larvae are eaten by large fish, such as perch, bass, carp, pickerel, etc., and the small fry cannot exist and fill their function unless protected from their enemies. In the second place, the eggs and larvae of the anophelines lie on or near the surface of the water and antimosquito fish must be top feeders. There are many species of small fish which feed only on the bottom. Of course, these are not efficient mosquito exterminators. The general term "*top minnows*" applies to the many and varied species which may be used in the antimalarial campaign. However, top minnows need man's help if they are going to be efficient in rendering him assistance. They abound, in the absence of their enemies, in shallow water and breed in shoals near the banks. They seem to be especially at home in stagnant water, but without man's help they cannot pass over even a few inches of dry land and find their way into isolated puddles, cow tracks, and similar places in which mosquitoes may breed; therefore, they must be dipped from their natural habitat and distributed in isolated mosquito breeding-places. It is also desirable that we recognize the fact that too much aquatic vegetation re-

stricts the fish in their movements and at the same time gives protection to the larvae.

The Artificial Transportation of Mosquitoes.—The mosquito has apparently not hesitated to avail itself of the improved and rapid methods of transportation employed by man. The express carries New Orleans mosquitoes to Washington and even farther north. It is said on good authority that the City of Mexico was free from these pests until the railroads were built from Vera Cruz and from the valley of the Rio Grande. Herrera states that during the summer time almost every train from the north brings many mosquitoes to the City of Mexico. These escape from the cars, take advantage of the abundant breeding places, and soon multiply excessively. According to Lounbury, the rail-

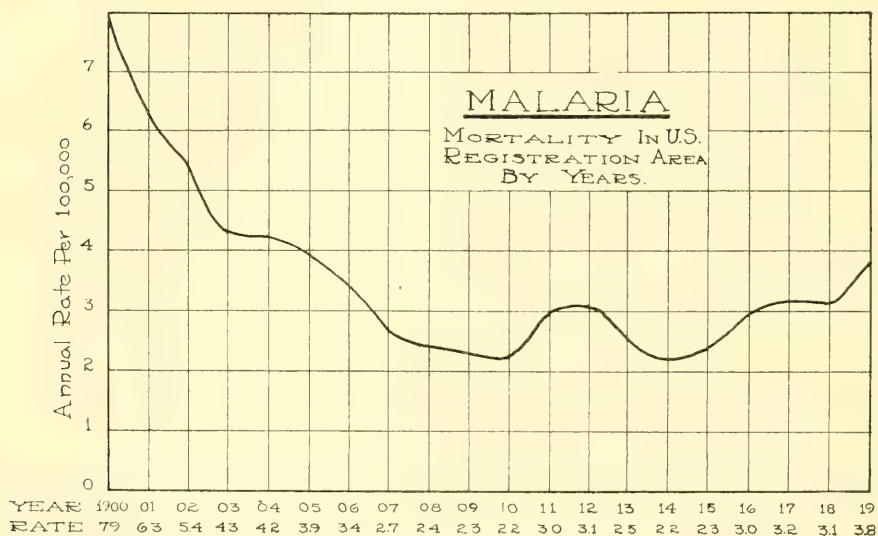


Fig. 33.

roads in Cape Colony have been efficient agents in the distribution of mosquitoes in South Africa. Like testimony comes of the distribution of these pests in Australia. Howard says that it is reasonably well established that Hawaii has no aboriginal mosquito fauna and that the mosquitoes found there were brought to the Islands in sailing vessels many years ago. The fearful epidemic of yellow fever in Philadelphia in 1793 was undoubtedly due to mosquitoes brought on sailing vessels from the West Indies; indeed, yellow fever was carried by sailing vessels as far north as Portsmouth, N. H. On the old type ship there was abundant opportunity for the breeding of mosquitoes. The introduction of steam has shortened the voyage but has increased the risk to the life of the mosquito which now would undertake a journey from

Colon to New York. At the same time the water-supplies of modern ships are more carefully guarded. Still the possibility, even under modern conditions of the transmission of infected anopheles or stegomyia from one country to another, must not be overlooked.

Measurements of Malaria Prevalence.—It is impossible to give any exact statistics concerning either the morbidity or the mortality from malaria in any country. As a rule, malarious countries are backward in their sanitation and do not provide for the collection and registration of sickness and death. The number of deaths from malaria reported in the U. S. Registration Area for the year 1919 is 3,275, corresponding to a rate of 3.8 per 100,000 population. This is the highest rate attained since 1905. In 1900 the rate was 7.9 and each year showed a decline down to 1910, when the rate was 2.2. There has been a general rise since 1915. The lowest rate reached is 2.2 for the years 1910 and 1914. The cause of the arrested decline is due, not to an actual increase in malaria, but to the changing character of the Registration Area. Most malaria is found in the southern states, and the recent additions to the Registration Area have come largely from the South. This will be illustrated in Table XXX.

TABLE XXX

YEAR	MALARIA DEATH RATE	STATES IN REGISTRATION AREA WITH YEARLY ADDITIONS
1900	7.9	Massachusetts, New Hampshire, Rhode Island, Connecticut, Vermont, New York, New Jersey, Maine, Michigan, Indiana, District of Columbia
1901	6.3	
1902	5.4	
1903	4.3	
1904	4.2	
1905	3.9	
1906	3.4	California, Colorado, Pennsylvania, Maryland
1907	2.7	
1908	2.4	Washington, Wisconsin
1909	2.3	Ohio
1910	2.2	Utah, Minnesota, Montana
1911	3.0	Missouri, Kentucky
1912	3.1	
1913	2.5	Virginia
1914	2.2	Kansas
1915	2.3	
1916	3.0	South Carolina, North Carolina
1917	3.2	Tennessee
1918	3.1	Oregon, Louisiana, Illinois
1919	3.8	Mississippi, Florida, Delaware

The rates for individual states have shown uninterrupted declines from 1900 to 1919.

TABLE XXXI
MALARIA MORTALITY IN CERTAIN STATES

YEAR	MASSA- CHUSETTS	NEW YORK	NEW JERSEY	MICHIGAN	KENTUCKY	VIRGINIA
1900	2.9	4.5	5.4	6.5	—	—
1901	3.2	3.8	4.4	4.6	—	—
1902	2.0	3.1	3.2	4.0	—	—
1903	2.2	2.1	3.1	2.6	—	—
1904	2.0	2.3	2.8	2.6	—	—
1905	1.4	1.7	2.4	2.3	—	—
1906	1.2	2.2	2.2	1.9	—	—
1907	1.2	1.7	2.0	1.2	—	—
1908	0.5	1.0	1.2	1.4	—	—
1909	0.7	1.1	0.9	1.0	—	—
1910	0.7	0.9	1.0	0.7	—	—
1911	0.4	0.7	1.0	1.0	10.3	—
1912	0.2	0.5	1.2	0.8	9.6	—
1913	0.4	0.4	0.5	0.6	8.1	7.1
1914	0.2	0.5	0.3	0.7	7.0	7.9
1915	0.2	0.4	0.5	0.4	6.4	7.0
1916	0.2	0.3	0.3	0.2	6.4	6.6
1917	0.1	0.3	0.2	0.2	5.7	5.6
1918	0.1	0.3	0.4	0.2	4.7	3.7
1919	0.1	0.2	0.1	0.1	3.0	3.0

States having rates above 10 per 100,000 in 1919 are Florida (43.7), Mississippi (36.5), South Carolina (31.7), Louisiana (26.6) and Tennessee (10.3). Other states with rates above the rate for the Registration Area as a whole (3.8 per 100,000) are North Carolina (7.9) and Missouri (6.4). Ten states show rates of 0.1 or less—Maine, Massachusetts, Michigan, Minnesota, Montana, New Hampshire, New Jersey, Pennsylvania, Utah and Wisconsin.

The eleven registration cities of 100,000 population or more with the highest death rates in 1919 were:

Memphis	31.4	Atlanta	2.0
Birmingham	6.2	Kansas City	1.6
New Orleans	4.4	Washington	1.4
Nashville	2.5	Spokane	1.0
St. Louis	2.3	Indianapolis	1.0
Louisville	2.1		

Of the 3,275 deaths from malaria in 1919, 2,760 occurred in the rural sections of registration states, 365 in the cities of registration states and 150 in registration cities in nonregistration states.

Differences in malaria prevalence between urban and rural districts are not so marked as one might expect. In the records of 11 states with significant rates in 1917, seven show an excess in the rural territory (towns with populations of less than 10,000). In Missouri the rural rate is from six to seven times more than in the cities. In North Carolina

the ratio is nearer two to one. In Virginia the rate in the cities is nearly double that in the rural sections.

TABLE XXXII
URBAN AND RURAL DIFFERENCES IN MALARIA MORTALITY—1917
ANNUAL RATE PER 100,000

STATE	URBAN	RURAL
California	0.6	2.3
Indiana	1.1	1.3
Kansas	2.7	2.0
Kentucky	4.8	5.9
Missouri	2.3	15.2
New York	0.2	0.4
N. Carolina	6.1	11.4
Pennsylvania	0.3	0.1
S. Carolina	22.7	35.3
Tennessee	19.1	19.1
Virginia	8.7	4.7

Mortality from malaria is about four times as common among the colored as among the white. The death rates in the registration area for 1917 (the last year for which rates are published in the U. S. Mor-

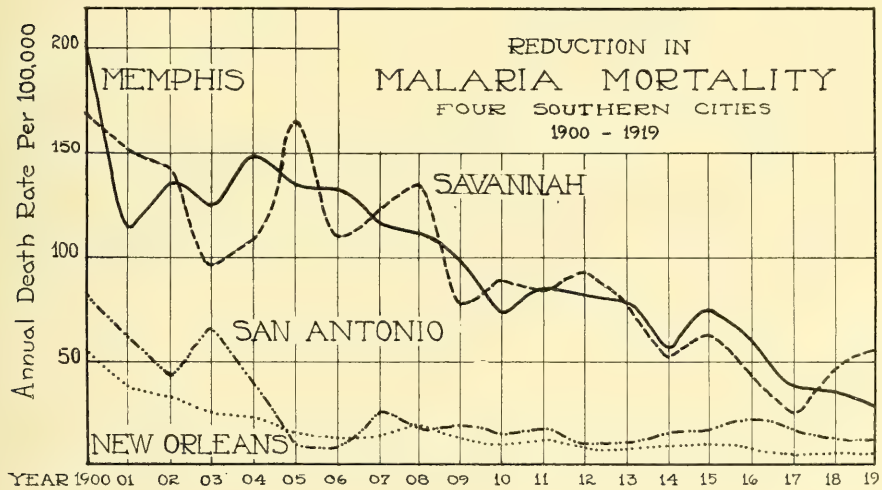


Fig. 34.

tality Statistics) show a much greater disparity than this, namely, 1.8 for white and 21.0 for colored, but this is not a fair expression of the racial difference. Most malaria is in the South, and the colored population is likewise found in greatest numbers there. The comparative figures for the entire registration area represent a large white population located for the most part in a nonmalarious section and a colored popu-

lation located principally in malarious sections. It is necessary to compare the white and colored rates within a state or city.

This we have done in Table XXXIII. Colored malaria rates exceed those for the white most markedly in Virginia, Birmingham and New Orleans, where the ratio is about 4.5 to one. The disparity is least in Missouri (1.5 to 1.0) and Vicksburg (1.8 to 1.0).

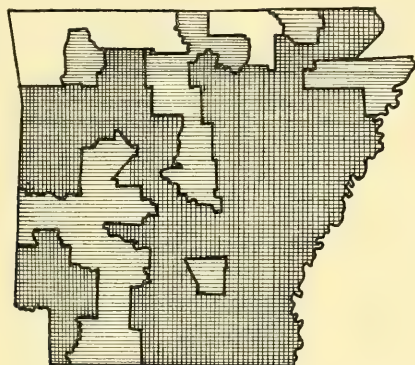
TABLE XXXIII
RACIAL DIFFERENCE IN MALARIA MORTALITY IN 1917

STATE OR CITY	ANNUAL DEATH RATE PER 100,000	
	WHITE	COLORED
Kansas	2.0	8.6
Kentucky	4.5	16.3
Missouri	10.1	15.4
North Carolina	7.0	19.8
South Carolina	12.6	53.2
Tennessee	14.7	36.5
Virginia	2.7	11.9
Birmingham, Ala.	5.0	22.7
Registration Cities of Florida	4.3	17.5
Augusta, Ga.	17.9	48.3
New Orleans	1.8	8.2
Shreveport, La.	23.2	58.1
Vicksburg, Miss.	53.5	94.0
Registration Cities of Texas	9.0	24.2

The death rate from malaria in Atlanta has fallen since 1910 among the whites from 4.6 to 1.5 per 100,000; among the colored people from 12.3 to 1.7. In New Orleans a corresponding fall has been among the whites from 9.4 to 1.8, among the blacks from 22.4 to 8.2; in Memphis from 55.6 to 20.5 among the whites and from 174.1 to 66.2 among negroes. In the smaller cities in the South, so far as we have figures, there has been a fall in the death rate from this disease among both whites and blacks, but this fall is not so marked as in the larger cities. In Vicksburg, taking the population as a whole, the fall has been from 138.1 in 1915 to 77.7 in 1917. Among these minor cities six have rates of 10 or more per 100,000 for the series of years 1911-1917: Mobile, Ala., Savannah, Ga., Paducah, Ky., Charlotte, N. C., Charleston, S. C., and Norfolk, Va. The five cities which have the highest rates in 1917 are: Vicksburg, Miss., (77.7); Brunswick, Ga., (63.7); Hattiesburg, Miss., (57.6); Meridian, Miss., (55.0), and Beaumont, Texas, (48.5).

In 1913 Carter made a report on malaria in eastern North Carolina, from which we make the following quotation: "In the absence of statistics I can only say that there is much malaria in eastern North Carolina, mainly of a rather mild type, tertian, but there is some estivo-autum-

nal. There is some in every town I have visited, generally in proportion inversely to its size, but varying, of course, with its environment. There is much more in the country, and of a severer type, than in the towns. Indeed a severe type, including much blackwater fever, is reported in several counties and small towns, none of which, however, did I visit.



MALARIA IN ARKANSAS

1915-1916

Heavy shaded areas indicate greatest prevalence

U.S. Public Health Reports
Jan. 25, 1918

Fig. 35.



MALARIA IN TENNESSEE

1913-1916

Heavy shaded areas indicate greatest prevalence

U.S. Public Health Reports
Aug. 27, 1917

Fig. 36.

These reports are from practitioners in Plymouth, Washington, Newbern, Goldsboro, and Fayetteville, who practice in the places where the severe type prevails."

In 1914 von Ezdorf made a survey of malaria prevalence in the states of Alabama, Arkansas, Florida, Kentucky, Louisiana, North Carolina, South Carolina and Tennessee. From the returns received he esti-

mates that 4 per cent of the population, or 600,000 people, in a total population of 15 million had malaria. Since this time more detailed studies have been made by the Public Health Service. The accompanying maps suggest the relative prevalence of malaria in the counties.

While eastern Tennessee, being mountainous, is on the whole relatively free from malaria, the western part of the state is badly encumbered by this disease. In 1917 tertian infection was reported in 31 counties, quartan in 21, and estivo-autumnal in 24. In South Carolina in 1915-1916 the malaria incidence reached its height in September. There was much estivo-autumnal fever, and as we have already stated, the death rate, especially among the colored people, is high. In Florida in 1914 Ezdorf found malaria in every county except one, and that did not report. The pernicious form of the fever is widely distributed throughout the state.

The Parasite Index.—There are several methods to follow in attempting to get data concerning the prevalence of malaria in any community. One of these is to determine the parasite index. This means the percentage of individuals in the community in whose blood malarial parasites can be found after a reasonable search by one expert in the procedure. It will be understood that this gives the minimum rate for the disease in the community. It can in no case be an overestimate. The number of parasites in the peripheral blood at the time of the examination may be so small that even an expert cannot detect them. In other cases quinin accounts for the failure to detect the parasite. The parasite index may be employed not only for determining the percentage of people infected in any community, but it may be applied to different groups of individuals; for instance, to villagers and farmers, to children and adults, to males and females, etc. In fact, this method is most applicable to children. The one making the survey visits the schools, talks to the children, and examines a drop of blood taken from the ear of each. It is also of value in the examination of employes in large lumber mills and elsewhere. To attempt this procedure by going from house to house is never satisfactory. Ezdorf has done some of this work among both white and black school children in Arkansas. In four village schools he examined 802 children and found the parasite in 6.6 per cent.

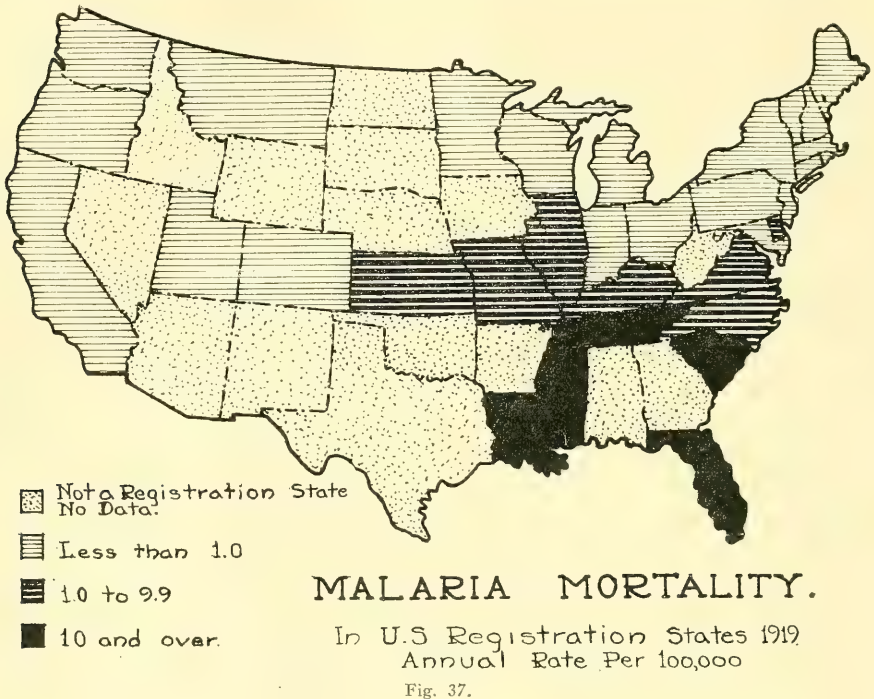
The Spleen Index.—This method of ascertaining the relative prevalence of malaria has been employed for a long time. As we have already stated, the connection between enlargement of the spleen and malaria was well known to ancient Greek physicians. The enlargement is sufficient to be easily discoverable in a few seconds by pressing the fingers under the ribs of the left side, and this can be done not only by physicians, but by assistants, nurses, and even by trained members of the

laity. The subjects with clothing properly arranged pass in line before the examiner, who reports the result to a secretary standing behind him. Properly carried out, 100 people can be examined in this way in an hour. Ross examined 31,022 children in Mauritius and 92,258 in Ceylon. As Ross points out, this method is open to certain defects: (a) In early cases the enlargement may not be sufficient to be detected in this manner. (b) In healthy infants the spleen is easily palpable occasionally. (c) Not all infected persons present a palpable spleen. (d) All persons with palpable spleens are not necessarily infected with malaria. In certain regions kala-azar must be excluded. The advantages in the method are evident and the information obtained is with due precaution sufficiently accurate. Ross found that the average child on the Island of Mauritius had a spleen 2.54 times the normal size. In this computation of course, normal spleens were counted. Omitting these the average enlarged spleen was 5.54 times the normal. The degree of enlargement of the spleen is believed by Craig to depend upon the kind of parasite and, according to this author, there is the greatest enlargement in estivo-autumnal fever. This has been questioned by Hope and others, who are inclined to the belief that the extent of the enlargement is dependent more upon the length of the continuance of the disease than upon the nature of the parasite. Craig's belief that the enlargement of the spleen is greater in estivo-autumnal infections than in either tertian or quartan is based upon his own personal studies of many thousands of malarial infections and is supported by the well-known fact that in estivo-autumnal infections the number of plasmodia is infinitely greater in the spleen than in tertian or quartan infections and immense numbers go through their entire life-cycle in this organ, thus causing pathologic changes leading to hypertrophy much more frequently than in other malarial infections. Long-continued malarial infection with any of the species of plasmodia will undoubtedly cause enlargement of the spleen but this occurs much more often and with greater rapidity in estivo-autumnal infection than in either tertian or quartan according to Craig's observation.

The Fever Index.—Of course, in using this measure one must be sure that the fever is malarial and not typhoid or due to some other infection. In regard to the value of the fever index, Ross makes the following statement:

“The admissions into military hospitals, civil hospitals and hospitals of gaols and plantations, are generally fairly correctly diagnosed by medical men, and give some idea of the great amount of sickness caused by the disease. The same is true of the large number of attendances for malaria at out-patient departments and dispensaries. The figures are valuable for comparative estimates of variation from time to time or place to place.”

Ross found in Mauritius that malaria caused 23.2 per cent of the total hospital admissions and 35.8 per cent of dispensary cases. In India before quinin was used to any great extent about 36.2 per cent of the soldiers were admitted to hospital each year for malarial fever. In highly malarious countries it is safe to say that one-third of the total population requires treatment for malaria each year. A few years ago, before quinin was so largely used, it was not rare to find on any one day during the malarial season twenty per cent of the employes on



sugar and rubber plantations sick from malaria. This gives some idea of the economic loss due to this disease.

The Geographic Distribution of Malaria.—It must be evident that malaria is not transferred in nature from one individual to another except through the agency of a mosquito of the genus *Anopheles*; therefore, the only cases of malaria that can exist in a country wholly free from these mosquitoes are those who come into the region already infected. As we have seen, these individuals may still carry the parasites in their bodies and may suffer relapses, but there can be no transfer of the parasite through natural agencies to another. On the other hand, there are many localities where *anopheles* abound but where malaria is not found. These mosquitoes acquire their infection only by biting

infected persons, and if there are no infected persons within their reach the mosquitoes never acquire or transmit the infection. Anopheles are still widely distributed over the Great Lakes region of the United States, but there is no malaria in this area unless some individual bearing the infection comes into it. This occasionally happens and there are local outbreaks of the disease. Laborers from Italy bearing in their bodies the infection come to this part of the United States and are bitten by mosquitoes, which transmit the parasite to others and local outbreaks result. It will be seen from this that only a general statement can be made concerning the geographic distribution of this disease. When we attempt to definitely define its limits it may easily be seen that malaria may appear next summer in places where it has not been seen in the past 20 years. Shipley writes as follows concerning the geographic distribution of malaria:

“Roughly speaking, malaria is confined to a broad irregular belt running round the world between the fourth isothermal line north of the equator to the sixteenth line south. It is, however, said to occur occasionally outside these limits—for instance, in southern Greenland and at Irkutsk in Siberia; but until recently the accurate diagnosis of the disease has been difficult, and too much reliance cannot be placed on these statements. The chief endemic foci of the disease are along the banks and deltas of large rivers, on low coasts, and around inland lakes and marshes. Malaria is common all around the Mediterranean region; it was well known to, and its symptoms were clearly noted by, the early physicians since the time of Hippocrates. They even recognized the difference between mild spring and summer attacks and the more pernicious effects of the autumnal fever. In France there are several prominent malarial districts: the valley of the Loire and its tributary the Indre, and the valley of the Rhone; also the seacoast and strip from the mouth of the Loire to the Pyrenees, and again the Mediterranean seaboard. It occurs in Switzerland, and is found in Germany along the Baltic coasts and on the banks of the Rhine, Elbe, and other rivers, and in many other parts. Scarcely a province in Holland is quite free from it, and it is found in Belgium and around Lake Wener in Sweden. It extends along the Lower Danube and around the Black Sea, and spreads across Russia, being especially prevalent along the course of the Volga and around the Caspian. From Europe it spreads over Asia Minor and affects all southern Asia as far as the East Indies, but in Japan it is curiously rare. It is also infrequent in Australia—where it is confined to the northern half of the continent—and in many of the Pacific Islands; and it is unknown in the Sandwich Islands, New Zealand, Tasmania, and Samoa. In America it is more common and of a more severe type on the Atlantic seaboard than on the Pacific; in the last hundred years its northern limit is said to have retreated in the center of the continent, though some observers think it is creeping farther north in the eastern states. In a mild form it is known around the Great Lakes and in Canada and in New England; but it reaches a high degree of intensity in the southern states, Mexico, Cuba, and Central America, where it probably played a greater part in ruining the projected Panama Canal than all the corrupt financing of the speculators in Paris. It extends through the warmer parts of South America and is known in a virulent form all over Africa except the extreme south.”

It will be seen that some of the statements made in the above quota-

tion, although they might have been true when written, are not at present trustworthy. At this time there is malaria in the Sandwich Islands. The statement that it is creeping farther north in the eastern states was true 30 years ago and for a very good reason which no longer exists. At present, taking the United States as a whole, malaria is rare in New England and when present is due to local conditions. Anopheles are still found, though in greatly diminished numbers over New England, but they have opportunity to infect themselves only when some infected person comes in from a malarious section. In New York, New Jersey, and Pennsylvania there is but little malaria, and this holds good notwithstanding the fact that malaria bearing anopheles are fairly

MALARIA MORTALITY BY AGE

U.S. Registration Area, 1910-1914
Rate per 100,000

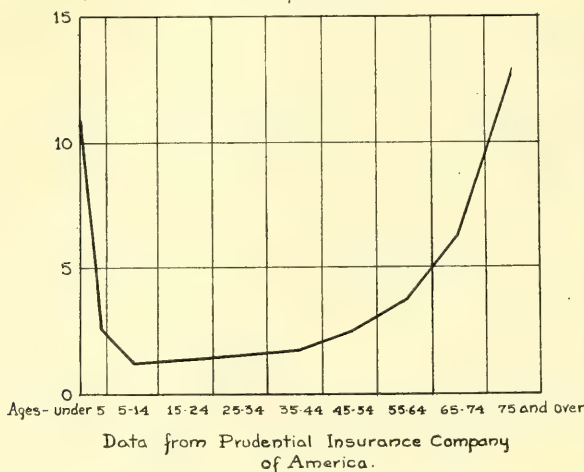


Fig. 38.

abundant in certain sections of these states. In Maryland, especially among the colored people, malaria is an important factor in causing both sickness and death. As we proceed farther south along the Atlantic Coast, and even if we spread out and cover all of that area south of the Ohio River and extend to the Rio Grande to the west, we include the great malarial region of the United States. The region round about the Great Lakes was 50 years ago highly malarious but now this disease is practically nonexistent. In California malaria has shown considerable variation in its prevalence for the past 20 years or more. This is due largely to the care or lack of care exercised in irrigation. This was foreseen long before we knew that the mosquito had anything to do with malaria by Widney, at that time secretary of the California State Board of Health, who wrote in 1881, as follows:

“The conclusion seems to be fairly just and legitimate, then, in the absence of any other apparent cause, and from what we know of the close connection between defective drainage and malaria, that in this case the relationship is that of cause and effect. With thorough drainage, the places which, by all other rules, should develop malaria, escape it almost entirely; without drainage, the places which, by all other rules, should be free from it, develop it constantly and actively. The whole history of irrigation in southern California goes to impress this lesson; that, to escape malaria, drainage must go hand in hand with irrigation; that unless it does, the water which brings wealth brings also disease and death.”

At about the time the above was written, Californians were busily engaged in lining their roads with plantings of Eucalyptus trees, with the hope that some mysterious exhalation from the leaves would neutralize some mythical gas to which malaria is due. The energy of the people has developed these roads into royal highways, but the malaria bearing mosquito now breeds in the pools that lie in the shade of the stately trees.

The Atlantic Coast of South America and the region extending far into the interior, even to the base of the Andes, are highly infested with malaria and in certain sections of this region the pernicious form is largely in evidence. The Pacific Coast of the same continent from Central America south is frequently dotted with malarial sections and in some places the disease has found its way high up the slopes of the Andes.

From the eastern end of the Mediterranean through Arabia and India and extending into the Malay Archipelago this is one of the most serious of diseases and has delayed the development of the people. The infection reaches in some places the lofty tablelands of the Himalayas and extends widely over southern China. The greater part of the African continent is involved and the pernicious form of the disease is found along both the west and east coasts of this continent. The infection has found its way into all the Islands of the Southern Pacific and the Indian Oceans. Northern Africa, including Algeria, Tunis, Tripoli, and the Nile Delta, is badly infested with this parasite.

While altitude constitutes a certain barrier to the progress of this disease, it reaches a height of more than 2,500 meters in the Andes. In the Himalaya Mountains it is found as high up as 2,000 meters. In Italy, Grassi has found certain malarial foci at an altitude of 2,500 meters. In Algeria it climbs to 1,800 meters. In Germany it has not been found above 500 meters. It will be seen from these statements that the altitude reached by this disease depends largely upon local conditions.

As is well known, the influence of settlement and civilization on this disease is variable, being dependent largely upon the attention that is given to drainage. Michigan, Illinois, Indiana, and Ohio, were 50 or

75 years ago highly malarious. In the sixties of the last century the rural populations of southern Illinois, Indiana, and Ohio, were almost universally infected. Quinin at that time was the only relief, but freedom from the disease was secured only after the establishment of satisfactory drainage. From 1906 to 1910 the average annual death rate from this disease in Indiana was 4.5 per 100,000. In 1917 it had fallen to 1.2. There is no satisfactory comparison for Illinois, since this state as a whole was not admitted to the registration area until 1918. In 1918 the rate was 1.3, in 1919, 1.4. Nuttall and his coworkers have made a careful study of the former distribution of malaria in England and the present distribution of anopheles. The malarial area was within but not so extensive as the anopheline area. The disease was severe in certain parts of England up to and including the early part of the nineteenth century. It began to decline about 1850, since which time it has entirely disappeared. The authors attribute the disappearance of malaria from England to (a) the reduction of anophelines by drainage; (b) to reduction of population by emigration, and (c) to the use of quinin. Ross thinks that (b) has had no effect, and he is inclined to attribute the disappearance of the disease almost entirely to the reduction of the anopheline factor by drainage and to the use of quinin. Furthermore, he seems to suspect that there has been some slight change in the climate not without effect, and that glass windows have been more in use since the beginning of the nineteenth century, thus lighting up the houses and destroying in a way the sanctuaries of the insects.

While there has always been more or less malaria along the Volga, in 1920 the disease in this region took on tropical form, with a high mortality; in some places fifty per cent. At the same time the disease spread even to the most northern parts of Russia and became endemic at Archangel. It should be stated that in these districts at that time quinin was exceedingly scarce and in some localities could not be obtained.

Preventive Measures.—The oldest method of personal protection from the annoying song and the bite of the mosquito concerned itself wholly with the desire of the individual to find for himself comfort and rest. As we have seen, mosquito nets were used by the intelligent long before the Christian era. Under the Latin name of *conopeum*, nets were employed by the Greeks and Romans, and possibly by still more ancient peoples. While some of the most observant, even in ancient times, apparently suspected that the mosquito might be the bearer of infection, it was not this suspicion that led man to protect himself from this pest by netting. Through all the centuries this method of protection has been employed more or less generally, and today it remains

an essential to the traveler who visits mosquito ridden countries. It is true that such a traveler might take quinin and thus render himself immune to malaria, but the quinin in his blood would not hush the song of his night visitor or prevent this predatory insect feeding on him. In the daytime in malarious countries netting is worn over the face and neck, while the hands and arms are protected by gloves. It is true that during the daytime one is not likely to be bitten by anopheles, but one is not desirous of being bitten by any species of mosquito. The mosquito net, however, has had its most general and efficient use

SEASONAL DISTRIBUTION OF MALARIA

UNITED STATES REGISTRATION AREA 1915-1919.
PER CENT OF ANNUAL DEATHS BY MONTHS.

Data adjusted to Months of 31 Days.

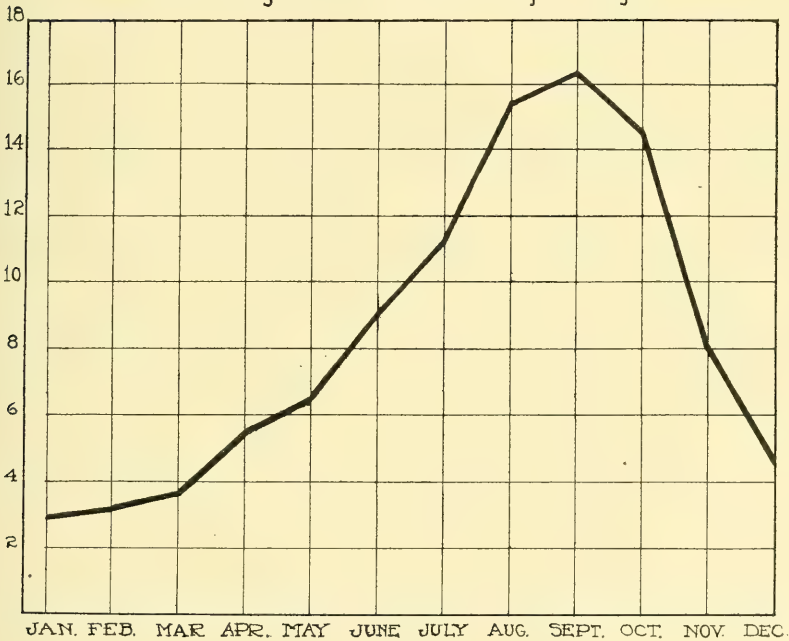


Fig. 39.

at night and covers bed or cot. It goes without saying that there must be no holes in it; that it should not hang to the floor, thus enabling mosquitoes in hiding under the bed to enter it, nor should it have any slit or opening in it. The net should not be thick enough to exclude the air and still must be fine enough to keep out the insects. About 18 threads to the inch furnish the best mesh. When small gnats are abundant the texture must be more dense and is best made of muslin or cambric. It should be stretched rather tightly, inasmuch as when allowed to hang in folds it excludes too much air. From the bed-net to

the room-net is quite an advance. Mosquito proof rooms large enough to hold the bed or cot, a small table and a chair, are now offered the traveler. Mosquito proof tents have been largely advertised and may serve a purpose in warm climates, but they are likely to be torn to pieces by winds or beaten down by heavy rains. Fortunately, it has become quite the fashion and the custom in this country to use screening in all houses during the summer time. This excludes not only mosquitoes, but other disease bearing and pestiferous insects. Verandas, doors, and windows are screened. For the verandas the screens are stationary and if made of the proper material and well cared for will last for years, especially when they can be taken down, stored away, and protected against the inclemencies of winter weather. A screened veranda gives comfort and protects from undesirable insect visitors, both day and night. It was found on the Isthmus of Panama where all screens must remain in place during the twelve months that it was cheaper to screen the verandas than to screen the doors and windows opening on to them. Screened verandas permit outdoor living both day and night and during the summer time constitute the most enjoyable part of the house. Screen doors are costly, demand some skill in their hanging, more frequently get out of order, and still more frequently through carelessness are allowed to stand open. Window screens are relatively cheap, easily placed, and when properly cared for will last many years. A 16-mesh screen will exclude anopheles but an 18-mesh is required to keep out stegomyia. It is possible to exclude anopheles with a 14-mesh screen, provided it is carefully painted, thus reducing the size of the mesh to about No. 16. If wire screens are painted every year or even once in two years and care is employed in their handling, they will last a number of years. As we have stated elsewhere, Sambon and Low lived in one of the most malarial sections of Italy during the worst season and escaped malaria simply by taking the precaution to enter their screened cottage before sundown and not to leave it before sun up. It should be remembered that for absolute protection against mosquitoes every possible port of entry into the house must be closed. These pestiferous insects will find their way through large key holes and will descend the chimney, entering the room through an open fireplace. The throat of the chimney can be effectively closed by packing with papers. In some instances the top of the chimney is covered with sacking and securely fastened. Wire screens might be used for this purpose and it would not be necessary to remove these when a fire is built.

In a report to the New Jersey Agricultural Experiment Station, Smith makes the following statement:

“Adjustable, folding, or sliding screens are never tight, and when the insects really want to get indoors they work their way patiently between the two parts of the screen

or between its frames and the window. But even a well-fitted screen either sets tightly into the frame or, running like a sash, may offer leaks when a window is only partly opened. There is abundant opportunity for the insect to get in between the net and lower cross bar; in fact, there is no real protection at all. Where the netting is fixed to the outside of its frame, so that there is no space between it and the lower part of the sash, the insects nevertheless find their way in between the window sashes. It has been already said that the mosquitoes will, in certain seasons, attempt to make their way through the screens, and they have less trouble with wire netting than with any other because the meshes are even in size and the strands smooth. Some of the fabrics used for nettings, specially of the cheaper grades, have threads so fuzzy that it is simply impossible for the mosquitoes to make their way through, and they rarely even try it except where there is a tear, or where the threads have been spread apart leaving an unusually large opening. Where an onslaught is made on wire netting it can be checked by painting lightly with kerosene or oil of citronella. I have tried both and found them successful.”

Not infrequently one neglects to screen cellar and attic windows and then wonders how mosquitoes find their way into the house. Whether they reach attic windows or not depends upon the height of the house, but that they are sure to find their way into cellar windows admits of no doubt. They are especially fond of the semi-dark corners and other hiding places found in the cellar.

Every fisherman has his special ointment with which he anoints his face and hands when he goes into the woods in search of trout. Each is confident that his own preparation is the only one which will protect from mosquitoes. According to Celli, the workmen in southern Italy rub their hands and faces with the fats of certain fishes or of certain kinds of game, or wash their hands and faces with infusions of certain plants, such as quassia, camomile, etc. Ross mentions oil of lavender, or eucalyptus, petroleum, ammonia, and powdered sandalwood, but he admits that these are not always efficacious. Laveran mentions sulphur, petroleum, a mixture of tar and oil, and quassia, but adds that his own experiences were unfavorable. Fermi and Lumbau tried many substances without evidence of success. Oil of citronella is used largely in this country and a mixture consisting of one ounce of this oil, one ounce of spirits of camphor, and one-half ounce of oil of cedar, has been largely used. According to Howard, a few drops on a bath towel hung over the head of the bed will keep *Culex pipiens* away for a whole night. The same author states that where mosquitoes are persistent a few drops of this rubbed on the face and hands will suffice. It is, however, of no value in protecting against the bite of the stegomyia. According to Howard, fishermen and hunters in the north woods will find that a good mixture against mosquitoes and black flies can be made as follows:

“Take 2½ pounds of mutton tallow and strain it while hot; ½ pound of black tar (Canadian tar). Stir thoroughly and pour into the receptacle in which it is to be

contained. When nearly cool stir in 3 ounces of oil of citronella and 1½ ounces of pennyroyal."

In regions around the Black and Caspian Seas and along the coast of the Mediterranean a powder known under various names, as Pyrethrum, Chrysanthemum, Persian Insect Powder or Dalmatian Insect Powder, has been used to kill insects. This powder is obtained from the dried flowers of certain species of the genus *Chrysanthemum* which grows abundantly in the Transcaucasia. The species now grown commercially is *C. roseum*. Howard says that 30 years ago it was considered the most valuable export of Dalmatia. The essential principal consists of oleo-resins and the strength of the powder disappears with age or exposure.

Asiatic and European species of these plants have been imported into this country and are now grown in California. According to Howard, the insect powders sold in the shops of this country have pyrethrum powder as a base but are largely adulterated. Under the United States Insecticide Act of 1910 it is now required that the manufacturers of insect powders indicate on the label the composition of the powder unless it is made from the flower heads of the following three species: (1) *Chrysanthemum cinerariaefolium*; (2) *C. roseum*; (3) *C. marshallii*. These powders are blown into crevices frequented by insects or are thrown into the air of a room in which there are mosquitoes or flies. It is a common practice to heap the powder into a pyramid which is lighted at the top and burned slowly, giving off a dense and pungent smoke. In recent years pastilles are molded from these powders and are sold in mosquito countries. It is a highly efficient method. It does not actually kill all the mosquitoes, but it paralyzes or stupefies them causing them to fall to the floor where they may be swept up and burned. It is not possible to get good results in clearing a room of insects with these powders unless doors and windows are tightly closed. The burning powder gives off a pungent but to most people not a disagreeable odor. There is a method of vaporizing its volatile oils without actually burning the powder. This is done by placing the powder on a metal screen above the chimney of a kerosene lamp and so regulating the distance that the heat volatilizes the oils without burning the powder. Howard states that he is in the habit of puffing the powder from an insufflator into a burning gas jet. Pyrethrum powder undoubtedly is of value as a means of clearing living rooms of mosquitoes. It has been used extensively in the fumigation of houses in epidemics of yellow fever; also to kill hibernating mosquitoes of all kinds in cellars, pantries, etc. The New Orleans Board of Health for a time recommended this method of disinfecting rooms during yellow fever epidemics. The Board required at first the burning of four ounces and later one pound for every 1,000 cubic feet. Finally, however, the Board withdrew the

authorization of this use of the powder, because the fumes do not kill the mosquitoes but simply stupefy them. Howard says:

“Nevertheless, on account of the fact that the fumes are not noxious to human beings, there still remains a decided use for pyrethrum in every day work in mosquito inhabited regions.”

During the outbreak of yellow fever in New Orleans in 1905 a chemist of that city recommended as a fumigant a mixture of equal parts by weight of carbolic acid crystals and gum camphor. The crystals were melted at a gentle heat and slowly poured over the gum, resulting in the preparation of a volatile liquid with an agreeable odor. In fumigation work three ounces of this is volatilized over a lamp for every 1,000 cubic feet of space. According to Berry, this preparation ranks next to sulphur as an insecticide in practical fumigation. A more thorough study by Francis led to the conclusion that the fumes do not penetrate readily and that large amounts of the compound are required to obtain satisfactory results.

Under the name of Pyrofume, McCormack of Mobile, has prepared by fractional distillation from pine wood, as a by-product in the manufacture of turpentine, a fumigant for mosquitoes. Francis, of the Public Health Service, in 1906, made a very favorable report on this insecticide, but for some reason it is not largely used.

Sulphur dioxid remains the most efficacious volatile insecticide. It is used in the ordinary way well known for general disinfection purposes. In the 1905 epidemic of yellow fever in New Orleans it was employed in the proportion of one pound to every 500 cubic feet of space. Rosenau found that even when present in the air in small quantities it kills mosquitoes and is quite as effective when dry as when moist. It has an unusual penetrating power and was found to kill mosquitoes hidden under four layers of toweling after an exposure of one hour. According to the same author, sulphur dioxid must be considered as holding first rank in disinfection against all mosquito-borne diseases. Formaldehyd gas has been tried and even recommended, but it was demonstrated soon after this gas came into use as a disinfectant that its insecticide properties are very feeble. It does not compare at all favorably with sulphur dioxid.

According to Celli, tobacco smoke is the most efficient volatile culicide. However, as we know from observation, while smoking may give partial relief from the persecution of the mosquito to the smoker, it is not possible to use this agent in ridding a room of these insects. The amount of smoke necessary to do this would be sufficient to thoroughly sicken the confirmed smokers in the room.

The volatilization of mercuric chlorid, 25 grams per 1,000 cubic feet of space, has been advised. Experimentally, this procedure has been

fairly successful. It is said that the vapors are without visible effect on man. However, when we remember that mercury may in relatively small amounts produce chronic poisoning, we are inclined to think it the part of wisdom to still prefer the old-fashioned disinfection with sulphur dioxid.

The Use of Petroleum.—Oiling waters prevents the development of mosquito larvae, because it cuts off the air supply. The oil forms on the water a scum through which the larvae cannot breathe. In selecting an oil for antimosquito purposes it should be borne in mind that the best kind will be that which spreads rapidly over the water and does not evaporate too quickly. The grade of petroleum generally known in this country as "light fuel oil" has been most commonly employed. Probably this is best known as "kerosene." An ounce of kerosene it is said will cover 15 square feet of water surface with a film sufficient to effectively destroy the larvae, and if it is not disturbed will remain effective for about ten days. Kerosene may be applied to marshes and pools by means of pumps or by hand sprays. On the Canal Zone the kerosene was carried in a tank on the back of the laborer and was thrown from a nozzle which he carried in his hand, much after the manner that the Hun in later years used his flame thrower. On small ponds and pools the kerosene can be distributed from a watering pot. It is evident that the removal of vegetation from breeding-places before oiling is desirable. If there be much aquatic vegetation there is great waste in oiling inasmuch as a large part of the oil floats on the plants, and, besides, a uniform pellicle does not result. If there be floating vegetable debris in the water the oil will adhere to it and may be moved even by moderate winds and leave unprotected surfaces of water in which the larvae may breed.

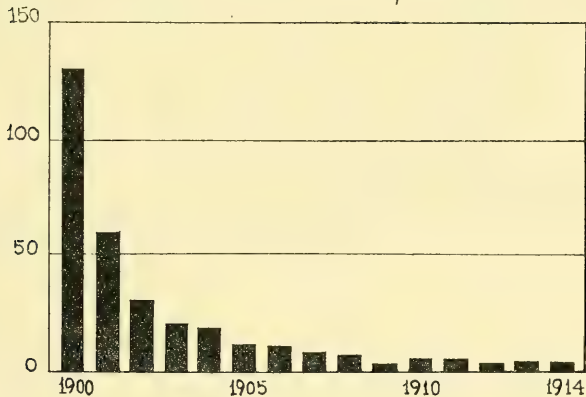
Experiments have been made with the desire to ascertain what oils are best in antimosquito work. Cheapness, tendency to spread evenly, and slowness in evaporation, are desirable points. An oil made from corn has been tried but it has been found not to compare favorably either in cost or effectiveness with kerosene. The present (1922) high cost of all grades of petroleum is limiting the use of oils in the extermination of mosquitoes and is turning attention more forcibly to the advantages of top minnows.

Larvicides.—On the Canal Zone, Gorgas, after abundant experience with these agents, concluded that there is nothing as yet known that is perfectly satisfactory. He states that an ideal larvicide should possess the following properties: (a) Low cost. (b) Ability to affect and kill mosquito larvae promptly, the more promptly the better. It must be effective in both still and running water. (c) The ability to dissolve, diffuse, and mix with water when applied to only one part thereof. It

must retain its larvicidal properties for a week or more, the longer the more valuable it is. (d) Diffusibility through water containing aquatic vegetation and vegetable debris. (e) Ability to kill green algae promptly. (f) It should kill mosquito larvae and pupae promptly in dilutions of 1-5,000. (g) It must not be poisonous to man or animals in solutions of 1-1,000. (h) It should so change the color of the water or give off a distinct odor so that people will not use the water for drinking purposes. (i) The odor must not be so obnoxious as to make it undesirable near habitations. (j) It should have a safe flash-test and be nonexplosive. (k) It should be sufficiently stable so that it may be kept standardized.

MALARIA MORTALITY IN HAVANA, CUBA

Annual Death Rate per 100,000



Data from Prudential Insurance Co. of America

Fig. 40.

Antimosquito Measures Employed in Havana.—For the sake of brevity we shall include here the destruction of both the *stegomyia* and the *anopheles*. Since the discovery of Cuba by Columbus yellow fever has been known as the curse of this island. For at least 150 years this disease had been endemic in Havana, from which port it frequently made excursions into the southern United States. Improved drainage and other sanitary measures reduced the total death rate in this city from 100 per 1,000 in 1898 to 22 per 1,000 in 1902. However, this reduction was due more largely to decreased immigration rather than to measures employed. Yellow fever prevailed in the metropolis of Cuba in direct proportion to the number of nonimmune population, and in 1900 there was a severe epidemic. When Gorgas took charge of this work the following species of mosquitoes were found to be abundant in the

city; *S. calopus*, *C. quinquefasciatus*, and *A. albimanus*. The first bred almost exclusively in the rain-water collections within the city. The second bred everywhere, and the third bred in pools and puddles in the suburbs, especially in those protected by grass. Gorgas organized two mosquito brigades, one to take care of the *stegomyia* and the other of the *anopheles*. The *stegomyia* brigade was confined to the city, which was divided into districts of 1,000 houses each. Each brigade consisted of an inspector and two laborers. The mayor issued an order requiring all collections of water to be so covered that mosquitoes could not have access, a fine being imposed upon those who neglected to obey this order. The city supply consisted of hard water, nearly every family collecting rain water in barrels. In the tenement houses each family had a water-barrel. The brigade covered these barrels with screens, permitting an opening for the gutter to discharge into the barrel, and placed a spigot near the bottom through which the water could be drawn. Nearly every house in Havana had a cesspool. Into these, the inspector poured from four to six ounces of petroleum and when the cesspool was not accessible the petroleum was poured into all closets connected with it. Barrels of fresh water found after a time not to conform to the law were emptied and the owner reprimanded. On evidence of renewed negligence he was fined. In January, 1901, there were found 26,000 fresh water receptacles containing mosquito larvae. In January, 1902, this number had been reduced to less than 400. The *stegomyia* practically disappeared and, for the first time in its history, the city was free from yellow fever.

So far as the adult mosquito was concerned the only attention given to it was by screening and by the fumigation of quarters in which yellow fever cases were found. Every case of yellow fever was carefully screened against the admission of mosquitoes.

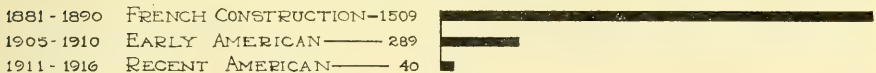
The *anopheles* brigade consisted of from 50 to 300 men and did its work along the small streams, in the irrigated gardens, and in other places where water might collect in the suburbs. No great engineering skill was required. The natural streams and gutters were cleared of obstructions and grass, and superficial ditches were dug so as to drain the irrigated lands. Pools of every size and description were obliterated. There was but little need for the employment of petroleum in this work. After a year it was rare to find mosquito larvae of any kind either in city or suburbs. In 1900, the year before this work was begun, there were 325 deaths from malaria. Today Havana is practically free from both malaria and yellow fever.

Measures Employed on the Canal Zone.—Gorgas, who had done such splendid work in Havana, was, fortunately, selected as chief sanitary officer of the Canal Zone when the United States undertook the digging

of the Canal. In the cities of Colon and Panama the conditions were much the same as had existed in Havana and the procedure adopted was similar. Upon first inspection in March, 4,000 breeding-places were discovered in the city of Panama alone. Within less than one year this number had been reduced to less than one-tenth. In Colon and in the villages between the two cities the same kind of work was carried out so far as the *stegomyia* is concerned. It is now universally admitted that the French failure to build the Panama Canal was not on account of lack of engineering skill, but because at that time they did not know how to deal with the mosquito. We have no figures showing the losses from yellow fever and malaria experienced by the French and their employes. The contractors, of whom there were 17, were charged \$1 a day for every sick man taken care of in the hospital. It was, therefore, to the interest of these contractors to discharge the sick as soon as possible. Gorgas thinks that there were more deaths among employes outside the hospital than in it. Many died on the roadside while en-

MALARIA MORTALITY AND THE BUILDING OF THE PANAMA CANAL

RATE PER 100,000 EMPLOYEES



Data from Prudential Insurance Co. of America

Fig. 41.

deavoring to reach either Panama or Colon. The superintendent of the old French hospital states that in one day three of his medical staff died of yellow fever and in one month nine. Of 36 Catholic sisters brought over as nurses 24 died of yellow fever. One vessel brought over from France 18 young engineers and within a month after their arrival all but one had died. Under the Gorgas administration, doctors with their families and the nurses, all nonimmunes, lived in peace and comfort and remained healthy in their well screened houses. Individuals sick from some other disease had no fear of lying in bed with a yellow fever patient on the next cot. The children of the medical and other officers maintained their health and grew at a normal rate and were quite as safe as they would have been in Washington.

Le Prince, who was chief sanitary inspector of the Panama Canal Zone under General Gorgas, has given us an account of the contest with anopheles in that region. This mosquito gave much more trouble and was reduced in numbers with greater difficulty than the *stegomyia*. Every known antimosquito method was used in the warfare with this insect. The screening of buildings was found to be of great impor-

tance, but even this was difficult to maintain in proper condition where ignorant laborers were concerned. The officers could protect themselves and their families by living in carefully screened houses. The nurses and patients were safe in the wards of the well protected hospitals, but the unskilled laborers, many of whom were ignorant West Indian negroes, were quartered in the native villages, lived in tents that had to be frequently moved, and sometimes slept in box cars. Protection against mosquitoes under these conditions was a difficult problem.

Gorgas states that his chief antimalarial work was rural, along a strip of land extending through the 47 miles between Panama and Colon. In this area there were about 80,000 people living within half a mile of the railroad and occupying some 30 villages and camps with more or less isolated houses scattered between. The 47-mile strip along the railroad was divided into 18 districts and each placed under the charge of an inspector whose duties consisted in carrying out the sanitary work of his district. Each inspector had at his disposal about 50 men. Gorgas estimates the importance of antimalarial work which he did as follows: (1) Drainage. (2) Brush and grass cutting. (3) Oiling. (4) Use of larvicide. (5) Prophylactic quinin. (6) Screening. (7) Killing mosquitoes in quarters.

In many localities drainage was exceedingly difficult. On the Zone the rainy period continues for seven or eight months. The dense vegetation prevents evaporation of surface water to a large extent and most of the ditches contain water throughout the wet season and partially during the dry season. Rains during certain seasons were almost daily, occurring 26 days out of the 30. Under these conditions it was difficult to keep open ditches free from vegetation, and especially from the rapid growth of algae. It was, therefore, necessary to resort to open ditches only when subdrainage was impossible. The rains helped to clean out the open ditches and to remove larvae, but heavy storms filled the ditches or obliterated them entirely. When of necessity open ditches were resorted to they were laid out on strict grade and lined with stone held in place by concrete. These ditches were in section a flat "V." The cost of maintaining open ditches was greater when they were not lined with stone. In certain sections there was much seepage water creeping out from the hillsides and keeping the lower levels most fit for mosquito breeding. In these instances subdrainage was found far superior in every way to open ditches. It was much more economical in the end than any other method employed. The open joints between the tiles were about one-eighth of an inch and the tiling was covered with pieces of field stone from four to six inches in diameter. With such tiling the flow of water in the drain carries the fine silt which enters through the joint, provided that the grade is about one per cent

for six-inch tile and not less than one-half of one per cent for ten-inch tile. When the ditches were dug the soil removed was thrown on the lower side of the ditch. It was necessary to keep the outlets of the tile cleared at all times. Gorgas states:

“The porous subsoil pipes give a perfect antimalarial drainage. Besides doing away with all breeding-places, they enable you to use a horse mower on the ground so drained, and thus much cheapen the cost of subsequent grass cutting. We use the open concrete ditch in localities where subsoil drainage is not practicable, such as flat places where the fall is not sufficient, and small natural rills where the volume of water is too large for subsoil drainage, etc. The objection to this style of ditch as compared with the subsoil is that it requires supervision for the purpose of keeping it free. Any obstacle in the ditch will make a small collection of water, which in this warm climate will breed mosquitoes at any time of the year. Open ditches we used only when the occupancy is going to be temporary, not more than two years. While the first cost is smaller than in either of the other class of ditches, the ultimate cost is very large. In a locality such as Panama, vegetation grows so rapidly that the ditches have to be cleared out at least once a month, and when clean they will breed larvae unless treated with larvicide.”

Each inspector was required to drain all pools within 200 yards of villages and within 100 yards of individual houses. Within the same areas all tropical undergrowth had to be kept cut. Gorgas considered this scarcely less important than the drainage, because brush and grass shelter the adult mosquito and the insect reaches a habitation from distant breeding-places by short flight so long as it can have continuous protection of vegetation. Moreover, the evaporation of surface water is largely increased by the removal of vegetation.

On large, low-lying, damp places where drainage was impossible it was necessary to use a larvicide freely. Le Prince gives the following method of preparing the larvicide found most efficient:

“Crude carbolic acid, containing about 15 per cent of phenol, is heated to 212° F., finely pulverized resin is added and the mixture kept boiling until the resin is all dissolved. Caustic soda is then added, and the solution kept at 212° F. for about ten minutes, or until a perfectly dark emulsion without sediment is obtained. The mixture is thoroughly stirred from the time the resin is added until the end. As the composition of crude carbolic acid varies greatly, the proportion of ingredients of the larvicide will vary, and it is necessary to have small experimental lots made in the laboratory, and tested before the batch of larvicide for use in the field is manufactured. The average mixture is about as follows:—300 gallons crude carbolic acid; 200 pounds resin; 30 pounds caustic soda.”

It was found that one part of this mixture placed in 5,000 parts of water containing mosquito larvae kills in less than five minutes, while one part to 8,000 kills in 30 minutes. In lagoons and ponds after the removal of the vegetation so far as possible from the edges, this larvicide was introduced in sufficient quantity to prevent breeding. In larger bodies of water dead vegetable matter is sometimes driven into wind-

rows and in these mosquitoes deposit their eggs. All such accumulations must be removed. The larvicide was distributed from knapsack sprayers, and each laborer could carry with him enough to occupy several hours of his time in spraying.

MALARIA MORTALITY
IN PANAMA CITY, C.Z.
Annual Death Rate per 100,000

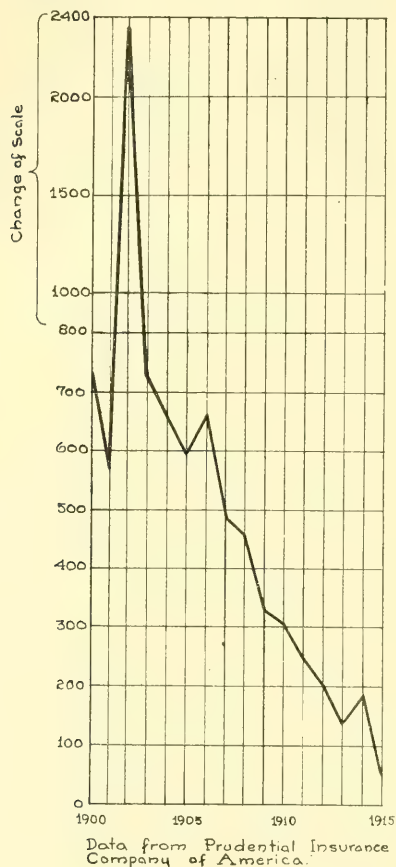


Fig. 42.

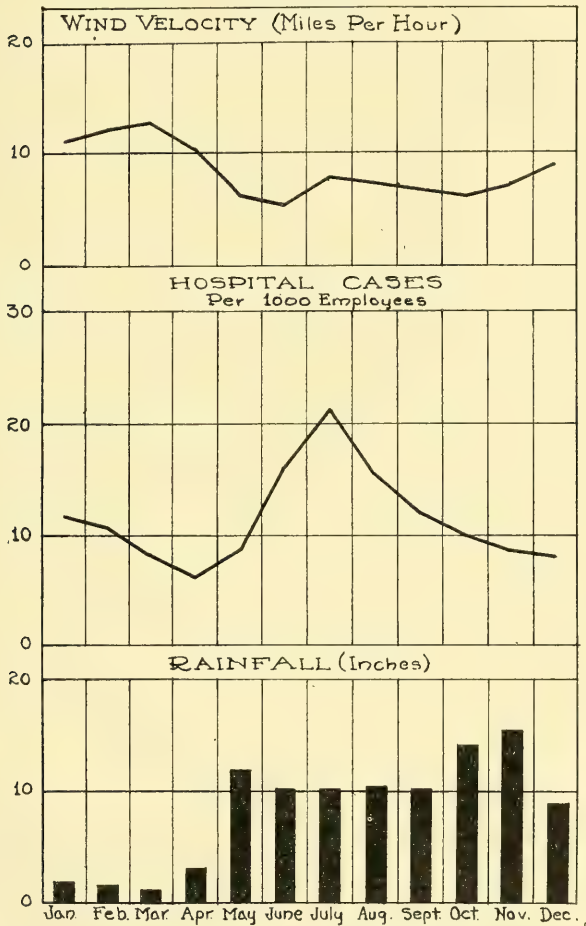
Le Prince makes the following statement concerning the use of oil:

“In long running streams and open ditches where antimalarial work is being done crude petroleum may be used, and it is more effective when applied automatically. Should the quantity of running water be small, so that not much oil is needed, then a handful of cotton waste tied in a bundle is soaked in oil for a day, and then placed near where the water outcrops. The water passing by this waste becomes covered with a very fine film of oil. The waste gives off oil film for about 10 to 14 days and is then

resoaked in oil and used again. For larger bodies of water having fair velocity, drip cans or drip barrels are used and should be located two feet above the water surface to break up the oil drops as they fall. They are made as follows:—a piece of metal similar to that of a flat wick lamp that holds the flat wick is fastened to the barrel or can near

SEASONAL VARIATION IN MALARIA MORBIDITY

PANAMA CANAL ZONE
1909 - 1913



Data from Prudential Insurance Co. of America

Fig. 43.

its base. This wick chamber is made somewhat larger than the wick, so that the wick may fit it loosely when saturated with fuel oil. The space inside the barrel, between the wick chamber and the bottom of the barrel, is filled with a solution of caustic soda or larvicide. As the oil passes along the wick it comes in contact with the caustic soda and is cut or rendered thinner. This prevents the wick from becoming clogged by

the thick fuel oil. The wicks seldom clog, but in case such occurs some larvicide is dropped on the wick. This cleans it, and makes it as serviceable as before."

There were 21 dispensaries along the line and all of these distributed quinin gratis. It was placed on all hotel and mess tables. Besides these methods of distribution, there was in each district a quinin dispenser who spent his time going from squad to squad and offering everybody a dose, allowing each to choose whether he should take it in pill form or in solution. There was no attempt to compel the taking of quinin. The annual use of quinin amounted to about 3,200 pounds, one-third of which went to the employes. Gorgas estimates that about one-half the force received a prophylactic dose of quinin each day. In addition to the above-mentioned measures, it was found profitable to have certain men engaged all day in killing adult mosquitoes in the tents, box cars, and houses in which the laborers slept. These mosquito killers went from tent to tent or house to house and destroyed all the mosquitoes found resting within. This killing was done by inverting a test tube containing cotton soaked in chloroform over the resting mosquito. This was regarded as a supplementary, but a justifiable, procedure.

Measures Employed in Rio de Janeiro.—The physical and social conditions in this city were adverse to sanitary measures when the work of eradicating yellow fever and reducing malaria was undertaken in April, 1903. At that time the city had a population of more than 800,000 and covered 430 square miles. Its topography is irregular, varying in altitude from 1 to 460 meters above sea level. It had a mixed population from all parts of the world, including many of the lowest classes, and occupying 82,396 houses. The Government made an annual appropriation of \$1,650,000 for the work. The personnel consisted of one chief administrator, one customs inspector, one accountant, seventy medical students, nine subchiefs, two hundred overseers, eighteen guards of the first class, eighteen guards of the second class, and about a thousand workmen. Cruz has reported on this work as follows:

"Yellow fever cases were made known to the sanitary inspectors by the reports of medical assistants, of the head of the family in which a case occurred, or by any one to whom the facts of the case were known, in accordance with the requirements of the law. The sanitary service being advised, a competent group of inspectors and authorities was at once dispatched to the locality, having with them a physician. The latter ascertained if the case was one for isolation treatment (whether under or over four days after the onset of the disease), and if the case required isolation the same was carried out either in the dwelling-house or in the hospital, hospital treatment being resorted to only when the dwelling was unsuited to isolation treatment or when the patient wished it. In such cases the patient was taken to hospital in a vehicle closed against the entrance of mosquitoes and the house was disinfected in accordance with the system below outlined. In the case of isolation in the home the physician chose a roomy quarter of the house, with a door opening into another secluded part of the house and with windows. If there were more than one door, the others were tem-

porarily closed. The patient was kept under a netting enveloping the bed upon which he lay during the time permanent quarters were being arranged. The doors and windows of the room to be isolated and of the rest of the house as well were sealed to prevent the exit of mosquitoes existing there, the windows of the isolated room being fitted with wire screens in such a way as not to interfere with ventilation, all other openings to the outside or to other parts of the house being sealed with cloth or paper. The only door to be used in the use of the room must be specially fitted with a double door drum, provided with an arrangement which does not permit of both doors being opened at the same time. This apparatus prevents the entrance and exit of mosquitoes, and after the room is thus prepared the doors and windows are closed and camomile is burned in the room three to four hours in the proportion of ten grams per cubic meter of space. The room is then well ventilated and is ready to receive the patient. The rest of the house is well calked and isolated from the room in which the patient is placed and disinfected with sulphur gas, as below indicated. During this operation the sanitary inspector remains in the room with the patient and stops the entrance of any gas which may possibly find its way through some overlooked crevice. During the preparation for disinfection the sanitary authorities make a thorough inspection and destroy any mosquito larva they find, pick up or destroy any vessels lying about which might serve as a receptacle for mosquito breeding-water and close water boxes against the same danger. The patient remains in isolation for seven days, after which isolation will terminate, if the family so wishes. The infected district is then treated as above indicated; that is, by disinfection, sanitary policing, and medical supervision. Disinfection is carried on in two ways, one force working from the center toward the outer limits of the district and the other from the boundaries of the district inward. The area of infection being determined over as large an area as possible, these two sections separate, one of which begins immediately with the house in which the case of yellow fever occurred, the other beginning at those houses which might possibly have been infected at the greatest possible distance from the case in isolation. The purpose of such a system was to destroy all mosquitoes which might have carried infection within the district. While the disinfecting force is thus at work the police division, under the direction of a physician and of students who direct the different sections, operates throughout the infected district, making every effort to destroy all mosquito larvae and to prevent the possible breeding of mosquitoes outside as well as inside the houses. Where larvae are likely to exist in stagnant water or refuse of any sort, petroleum mixed with creolin, lysol, or similar products, is thrown over the water or refuse in sufficient quantity to kill the larvae instantly. Where it is impossible to use petroleum, as in the case of tanks and boxes for household use, a small fish, the 'barrigudo' or '*Girardinus caudimaculatus*' is placed in large numbers in the water. The fish destroy the larvae of mosquitoes most voraciously. Larvae in the drains are destroyed by the use of Clayton gas, which is pumped into the sewer, which has been previously divided into compartments. Simultaneously with the disinfection the sanitary inspectors make daily inspection of the suspected district, examining every inhabitant supposed not to be immune; that is, children under five and all foreigners of less than five years' residence in Rio. These are subjected to the closest vigilance, being placed in isolation at the least tendency to rising temperature. Reports are made in writing, those to whom this duty falls being required to fill out daily a bulletin sent out by the medical inspector to the chief of each district. In this report must be given the record of any who work outside the district or who for any reason absent themselves therefrom, a record of their condition being also kept by the physician in the district in which they work or are temporarily resident. When any inhabitant absents himself from the district the record must show his address, where he will be sub-

jected to vigilance on the part of the authorities there. If the person under vigilance evades the attention of the physician and withdraws without giving notice, the owner of the house in which he lived is fined, he himself is apprehended by the sanitary police, fined, and subjected to renewed vigilance. The vigilance in each district extends over a period of one month after the appearance of the last case. To give an idea of this service we will note the figures covering the prophylactic campaign in the infected district about the cotton factory, 'Fabrica das Chitas,' in 1906. The inspection was carried out by 18 doctors, who examined daily all suspected persons, in all, 7,966 persons, of whom 2,989 were not immune. Sixty cases were reported, of which only 19 proved to be yellow fever, and the district was declared entirely freed of infection after six months. With the combination of the three systems there is no doubt about cleaning up effectively any district in which yellow fever may appear. In normal conditions the police service is carried out with equal painstaking, especially in the districts where infection last appeared. When, after some time, there seems no longer to be danger of new infection, the inspectors allow water to stand in several marked spots most favorable to mosquito breeding. These pools are then carefully watched, and examined at frequent intervals. This is a sure way to indicate the presence of the mosquito and is a trap for those about to spawn. They are thus most easily destroyed. In many zones of the city these traps revealed the presence of no mosquitoes whatever."

In 1901 there were 2,299 deaths from yellow fever in Rio de Janeiro. In 1909, for the first time since records have been kept, there was not a case.

Antimalarial Work in Italy.—Under the splendid guidance of Celli, Italy during the first 15 years of the present century was making giant strides in ridding itself of mosquitoes and in improving living conditions of its laboring classes; indeed, we think that it may be said with truth that during the time mentioned, Italy did more than any other nation in protecting and improving the health of its people. The Government not only concerned itself with the welfare of Italians at home, but every ship carrying Italian emigrants to North or South America was compelled to carry an Italian health officer, who looked after the quarters and food of those under his charge during the voyage. Moreover, Italy attempted to protect its emigrant children after arrival in the Western Hemisphere and to save them, so far as possible, from exploitation.

In his fight against malaria, Celli spoke of his triple alliance, the doctor, drainage, and agriculture, and claimed that this combination was able to thwart the most formidable enemy of his country. He saw that there had been established in Italy a vicious circle whereby man could not live on the land because it was malarious, and the land could not be rendered healthful because man was unable to live on it. With great wisdom Celli saw that the most speedy and effective method of rendering the Italian peasant fit to live, or at least able to live in his country, was by the administration of quinin. Under the temporary protection of this agent the people would be given strength and afforded time to

provide drainage and establish profitable agriculture. In 1900 state quinin was placed on sale at cost price. In 1901 laborers were provided gratuitously with state quinin *for treatment* of malarial fevers. In 1904 laborers were supplied gratuitously with quinin *for prophylaxis*. Until the World War came and interrupted this most beneficial work the consumption of quinin in Italy went up year by year, while in the same ratio the mortality from malaria fell. Simultaneously with the temporary protection secured by quinin the Government encouraged protection of its laboring classes from the mosquito by mechanical means (screening) and the eradication of the insect by drainage and scientific agriculture.

We are surprised that Celli finds that prophylaxis against malaria is secured by the daily use of such small doses of quinin as 50 centigrams. This is a matter of so much importance that we reproduce at some length his conclusions:

“(a) That quinin, provided it be *administered* daily, is in average and even therapeutic doses better tolerated, and for a longer time than *a priori* one could have believed; that is to say, after the first two or three days it no longer produces the least ringing in the ear, and is not only completely innocuous, but also acts as an aid to nutrition and as a tonic to the digestive apparatus and muscles, thereby increasing the appetite and the power of work. (b) Quinin taken daily is always present in the blood, and thus prevents instead of producing the phenomena of quininism. Further, there is not, perhaps, another example of a remedy so perfect, nor one which so rapidly establishes itself, and can be prolonged for a long time (up to five or six months), and yet can be interrupted when desirable without any disturbance, and without, although the organism is habituated to the small and average doses, diminishing the curative efficacy of the large doses when they are necessary. (c) But if quinin be given at intervals longer than three days the phenomena of quininism present themselves every time; in consequence the method of intermittent administration, namely, every four days (Ziemann), every five (Plehn), every seven to ten (Koch), although recommended by these able workers, is not preferable to our continuous and daily method. The administration at intervals of every two or, at the utmost, of every three days (Sergeant) may be in some cases employed. Longer intervals are not to be recommended, owing to the disappearing of the quinin from the blood three days after the administration. (d) Intolerance to the salts of quinin insoluble in water, if they be administered in average doses daily, is met with in very few persons, and up till now we have never observed the hemoglobinuria which the intermittent method and the relative large doses have not succeeded in preventing. (e) Intolerance very exceptionally manifests itself if a salt insoluble in water, such as tannate of quinin be given. This salt is slowly absorbed, especially in the intestine, by the work of the bile and of the pancreatic juice, and it is perhaps for this reason that it has the value of being generally atoxic, even in persons who have a special idiosyncrasy for hemoglobinuria towards the salts soluble in water. By reason of this ordinary atoxicity, as well as the absence of bitter taste, it is specially indicated for children, and for those adults who show intolerance for the other salts or suffer from malaria complicated by gastrointestinal disturbances. (f) According to Mariani and Giemsa also, quinin proper that is, in the basic state, is absorbed and acts very well. Consequently, the solubility or not in water of a preparation of quinin, or its administration with the stomach full or empty, do not in the least deserve that importance which has been and is attributed to them.

(g) An essential coefficient of true tolerance is to administer it in an agreeable form, hence the forms of comfits or chocolates which we have persistently proposed for the various salts of quinin. (h) He who takes quinin every day, and therefore has always a supply of quinin in the blood stream, *can undergo with impunity inoculations of blood full of malarial parasites*, and can expose himself with little or no danger to the bites of infected mosquitoes. (i) Arsenic and iron do not display any protective anti-malarial action, either experimentally or chemically demonstrable.

“These are the scientific and practical facts on which we have based the method of preventing new infections, and of reducing the recurrences by means of the daily administration of quinin in average doses, namely:—40 centigrams of the bisulphate, hydrochlorate or bihydrochlorate of quinin for adults and young persons; 20 centigrams of the same salts, or 30 centigrams of tannate of quinin for children; and in every case administered in the agreeable form of comfits or of chocolates. These, especially, owing to the sugar and cocoa have overcome the dread and prejudice against the prophylactic use of quinin.”

According to Cruz, Celli's method, including his small dose daily administered, has proved satisfactory among the railroad builders in Brazil. To these workers a daily dose of 50 centigrams of the hydrochlorate of quinin is administered by the doctors who see that the patients swallow the capsules. “Not one of the persons subjected to this regime fell sick, whereas others who accompanied the party without belonging to it, and who would not submit to the same prophylaxis, were attacked by malaria.”

The same observer reports that when these laborers left the malarial region and without reinfection, they developed malaria if they discontinued the use of quinin. Furthermore, if after leaving the malarial zone they continued the daily use of 50 centigrams of quinin for some months and then discontinued it they developed malaria without reinfection. One concludes from this that with this mild treatment the parasite remains alive but inactive in the human body.

It is now generally admitted that quinin should be administered as a prophylactic in daily doses of 60 centigrams if good results are to be obtained, as the smaller amounts simply kill off enough plasmodia to prevent the development of symptoms in a large majority of cases, but they do not actually prevent infection.

Work in Greece.—We have elsewhere referred to the possible connection between the introduction of malaria and the decline of ancient Greek civilization. Savas has published the results of recent surveys in that country. He states that twenty-nine per cent of the people are affected by this disease every year, and that from time to time there are exacerbations in which the infection is even more prevalent. In 1905 more than half the inhabitants of the country had the disease and more than 6,000 died from it. Before the war Greece was divided into 69 provinces and in 19 of these the infection annually touched more than forty per cent of the population. There are in Greece 639 marshes not

counting those covering areas of less than 1,000 square meters; indeed, marshes occupy from one sixty-eighth to one seventy-second of the whole surface of the Kingdom. In addition to these large marshy areas there are innumerable smaller ones and there are streams in which pools are formed during certain seasons of the year.

Savas gives a most interesting picture of the present condition of the classical Plain of Marathon. This lies on the east coast of Attica about 30 kilometers from Athens and is 11 kilometers in length. In 1910 the population of the Plain of Marathon numbered 1,680, distributed in villages each containing not more than 200 inhabitants. The village of Marathon itself had a population of 1,200. In this village in 1906 the school children were examined for enlarged spleen and this condition found to be present in one hundred per cent. The whole of the plain at certain seasons of the year is covered by two large marshes and innumerable small accumulations of stagnant water, in all of which the larvae of anopheles were found. The Greeks first tried the German method of employing quinin both for curative and preventive measures. This method consists in giving one gram of quinin on each of two successive days and then permitting an interval of from seven to nine days, when the doses are repeated for two successive days. This method of using quinin was found to be impracticable for two very good reasons. In the first place, the large dose causes great discomfort, such as ringing in the ears, dizziness, drowsiness, and general weakness. In the second place, during the interquinin periods people become infected with the disease. This method of employing quinin should not be regarded as proper prophylactic treatment. It results in systematizing regulated curative treatment. After finding that this method did not work, the Greeks resorted to the method of Celli which consists in the administration of 50 centigrams of quinin daily. This form of administration keeps quinin constantly in the blood and thus protects at all times against inoculation by the mosquito. In the second place, it does not induce quininism. There are no unpleasant effects. The guard is on duty all the time and never harms his ward. We think it safe to say that the different methods employed with quinin as a prophylactic against malaria have been sufficiently tried in various parts of the world to justify the conclusion that the Italian procedure is the most satisfactory and the most efficacious. In 1910 the Government of Italy was supplying Greece with quinin at cost. So far as we know, the Greek Government has never supplied its poor with quinin gratuitously. We do not wish to be understood as recommending the employment of quinin in all antimalarial work.

In the early part of the present century Pankrati and Batraconesi, suburbs of Athens, suffered severely from malaria, the average percent-

age of infection running from 30 to 50 and occasionally going as high as 90. Malaria in these villages was due to small pools in the bed of the River Ilissos. These were found to be filled with larvae of *A. superpietus*. In 1906 the river bed was converted into a narrow channel and the stagnant pools filled. This simple and relatively inexpensive procedure sufficed to abolish malaria. It was not necessary to resort to the prophylactic use of quinin.

Work in Malaya.—Watson has written a most interesting volume on the antimalarial work in the Federated Malay States. This enterprise was undertaken in 1901 along the Klang River and at Port Swettenham. Different regions in the Federated Malay States are occupied by different species of anopheles and present widely variable problems when the eradication of malaria is undertaken. It has been found that, while removing the jungle and letting in the sunlight causes the disappearance of *A. umbrosus*, it invites the coming of *A. maculatus*, and malaria transmitted by the latter is just as bad as that conveyed by the former. On the whole, deforestation and subsequent drainage have been the most effective measures tried in Malaya. Clearing out the jungle and even the stripping of the jungle land of all its growth, unless accompanied or followed by drainage, has not succeeded in eliminating malaria. Watson emphasizes the facts that a scheme suitable for the eradication of one species of mosquito is not necessarily suitable for another; that methods found successful in the case of *A. umbrosus* proved worse than useless in the case of *A. maculatus*; that schemes suitable in one country should not be slavishly followed in another where the mosquito fauna is different; that a thorough mosquito survey is an essential preliminary of any scheme of eradication, and the scheme should be framed according to the mosquito findings; that a problem full of indeterminate elements must be tested by trials and experiments; that unforeseen difficulties are likely to arise whatever the scheme adopted and, finally, that the cost is at the start a guess and generally grows with the progress of the work. At certain localities, both in the Federated Malay States and in India, procedures for the eradication of malaria adopted without proper preliminary study have ended in making matters worse. Watson says that some years ago the Royal Society of England and the Government of India joined forces in an attempt to eradicate malaria from Mian Mir, with the result that after much money had been spent the cantonment was more malarious than ever.

We cannot refrain from giving the following quotation from Watson concerning man's warfare with the tropical jungle:

“Against the intruder, the jungle wages a ceaseless, though silent, warfare. It neither sleeps nor slumbers; and if it is to be kept in check, it requires of man endless effort. Ever vigilant, it sends forward, at every opportunity, its advance battalions.

Along the drains creep the water-loving grasses and rushes; on their sides soon appear other grasses and tiny ferns. Grasses, ferns, wild bananas, and bushes grow on the dry ground of the ravines. Gradually leaves, sticks, and silt obliterate the drains; the ravine reverts to its original swamp, the ferns and bushes are replaced by the trees of the original forest. The jungle comes into its own. With all these changes, the insect life of the ravine changes too: at one period the insect inhabitant may carry disease; at another period it may be harmless. And one zone differs from another. It is in the power of man temporarily to arrest these changes at any stage favorable to himself, or to allow them to march to their destined end.''

Antimosquito Measures in the United States.—As we have already stated, malaria has practically disappeared from the northern part of our country, and, indeed, the northern boundary of the malarial region has been constantly but slowly withdrawing to the south during the past 60 years. Until 1900, however, all the antimalarial work done in this country was for the purpose of reclaiming valuable land. There was no thought of the prevention of malaria, nor, except here and there, any of antimosquito measures. The farmers of Michigan, Wisconsin, and adjoining states found that the marshy districts and tamarack swamps contained the most productive soils, and consequently they proceeded to drain these areas, strip them of their worthless vegetation, and put them under cultivation. Now these areas are yielding great annual revenues in crops of celery, sugar beets, peppermint, pennyroyal, etc. Sections of land in Michigan which 60 years ago were not only unproductive but were the hatching places of innumerable anopheles, are now worth hundreds of dollars per acre and are making their owners rich by the annual production of tons of sugar beets. In 1880 the death rate from malarial fevers in Michigan was 19.5 per 100,000. There were actually 320 deaths from this cause. In 1919 there were 5 deaths charged to malaria, an annual mortality rate of 0.1 per 100,000. This is a striking one of many illustrations which shows that improvements in health conditions have been secured as by-products in the production of wealth. Poverty, ignorance, and disease have been and continue to be the most powerful obstructions in man's progress towards better things. It may be that the desire for wealth is a great curse, but it cannot be denied that in his pursuit of riches man has found many things more valuable than that which he sought. We are inclined to complain somewhat bitterly because the pine barons were permitted from 50 to 75 years ago to rob Michigan and adjoining states of their splendid and boundless wealth represented at that time in their magnificent and extensive forests, but while the pine robber committed his depredations, sometimes with the connivance of the administrators of the law and sometimes against their protests, he was unconsciously preparing the land for the more productive crops of the future, and at

the same time rendering the region a more healthful and habitable place for coming generations.

About 1901, the discovery of Laveran in 1880 and that of Ross in 1897, began to be known, appreciated, and utilized the world over. In this movement our country has not in all times lagged in the rear. We are not now speaking of the splendid work in preventive medicine done by our army medical officers in Cuba, Porto Rico, the Canal Zone, and the Philippines, but we are giving our attention to the work done in Continental United States. It is not possible to say just where this conscious effort first came into evidence; indeed, there is no one locality and no one individual that stands out preeminently in this movement. We shall, therefore, make no attempt to discuss chronologically the events which we are about to mention. At the same time it will be best not to inquire too minutely into the motives which prompted the anti-mosquito work of the first years of the present century. Howard says that one of the finest, most extensive, and most effective bits of this work was accomplished through the use of large sums of money furnished by a wealthy man whose object was not primarily the improved health of the people of the region, but to better the condition of his high-priced race horses which were suffering from the abundance of mosquitoes. In many other instances the basic purpose was to so improve mosquito ridden areas that the land could be sold greatly to the profit of certain individual owners or corporations.

In 1902 wealthy owners of Center Island, off the north coast of Long Island, under the corporate name of "North Shore Improvement Association" did splendid work, especially in demonstrating the feasibility of controlling and even eradicating the salt marsh mosquito.

In 1902 the Brooklyn Board of Health began a local campaign in which pools, ponds, ditches, and other breeding-places within and about the city were filled, drained, or oiled. Here and there all over the country local antimosquito brigades were formed. Hodge and McKibben did splendid work in Worcester, Mass., as did Langford at San Antonio. In 1903 there were a few cases of yellow fever with some deaths in the latter city. The people as a whole cared very little for yellow fever nor did they mourn very seriously over their dead neighbors, but the report that yellow fever existed in San Antonio caused a commercial loss to that city of many hundreds of thousands of dollars. After the common method of that time, the first thing the authorities did was to deny that there had been any yellow fever in the city. The next thing they did was to deny with equal vehemence that if it were yellow fever, mosquitoes had anything to do with it. They had lived, suffered from, and fought mosquitoes, for years; then why should the yellow fever of one year have anything to do with their old friends and enemies—the local mos-

quitoes? It was difficult to meet arguments of this kind. Langford, who was chairman of the Sanitary Committee of the School Board, had a bright idea. He had an aquarium placed in each school building and in these he bred, under proper precautions, mosquitoes, demonstrating to the children day by day and hour by hour the development of the eggs, the antics of the wrigglers, and the wonderful evolution of the pupa. Boys and girls were furnished with magnifying glasses and studied these interesting things in the tank, made drawings on the board, and then sought the natural breeding-places of these insects in and about the city. Prizes were offered for the largest number of mosquitoes captured and for the best essays. The children with these demonstrations before them were not influenced by the arguments of the adults and they went forth and exterminated the mosquito. There has been no death from yellow fever in San Antonio since. Before that time there were from 50 to 60 deaths each year from malaria. During the first year the mortality from malaria was reduced seventy-five per cent and in the second year it was entirely eliminated from the mortality records of the city.

In 1901 a house to house visitation of certain sections of Staten Island in New York Harbor showed that at least twenty per cent of the inhabitants of these districts were suffering from malaria. Breeding-places in the shape of barrels, cisterns, and puddles were abundant and were occupied and utilized by busy anopheles. Doty, then health officer of the port of New York, undertook the eradication of malaria from Staten Island. In 1905 he induced the Department of Health of the City of New York to cooperate in this movement and within the next few years more than 1,000 miles of ditches had been dug and malaria had practically been eradicated.

Excellent work has been done by state entomologists and boards of health. Smith, entomologist for the State of New Jersey, deserves especial mention in this connection. He induced that state to pass a law which provided for a survey at the request of the local board of health of any city, town, or township. In this survey all mosquito breeding-places were plotted. The law stated that these should be eradicated by the owner, provided that the cost of the work should not exceed the value of the land, in which case the state contributed not more than fifty per cent of this cost. By 1910 there had been reclaimed in the state not less than 30,000 acres of marsh land which necessitated ditching to the extent of about 70 miles.

The International Health Board has been and continues to be a most efficient agent in stimulating state and local boards of health in antimalarial work. This Board, first organized to combat hookworm disease in the south, seriously undertook antimalarial demonstrations

in 1916. The method of the board is to send experts into a highly malarious community to demonstrate to the people how the disease may be lessened. In one locality screening alone will be employed. In a second, the prophylactic use of quinin will be resorted to; in a third, killing adult mosquitoes in the houses is depended upon; in a fourth place antimosquito measures will be employed, and these vary according to the locality. It is desirous that the demonstrations show not only that malaria can be greatly reduced, but that the cost is within the means of the people. It is pleasant to note that in this work the representatives of the Board have had, in the main, the whole-hearted and enthusiastic approval and help of local physicians, notwithstanding the fact that the success of the work greatly decreases the income of the physician.

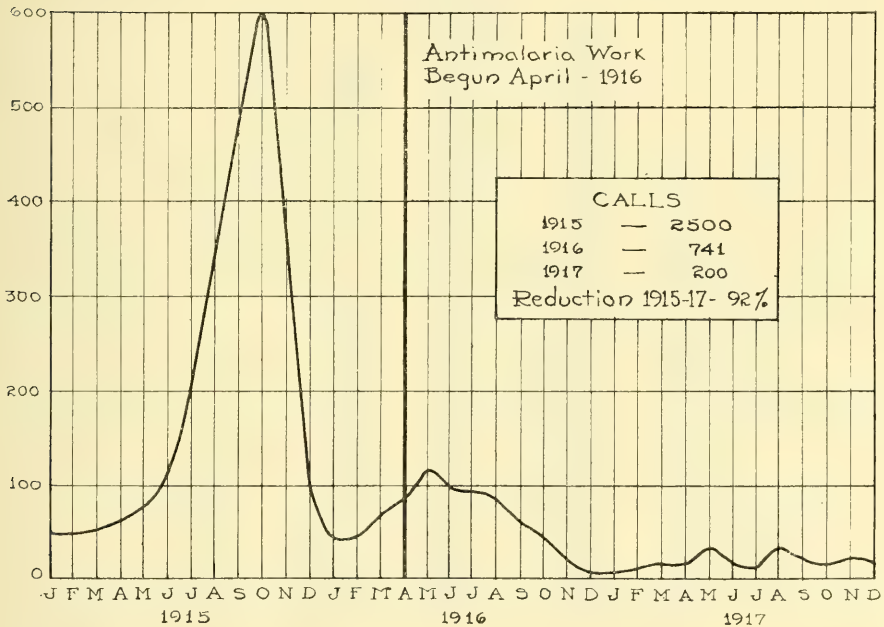
At Crossett, Arkansas, a lumber town of 2,029 people, antimalarial work was begun in April, 1916. This consisted in the elimination or control of the breeding-places of mosquitoes without major drainage. Pits and shallow ponds were filled or drained, streams were cleared of undergrowth, accumulations of debris were removed from the beds and they were regraded so as to permit an unobstructed flow through a narrow channel. Artificial containers were removed or treated. All other breeding-places were sprayed once a week with road oil. No other antimalarial measures were employed. The results as measured by physicians' calls are pictured in the chart. There were 2500 calls in 1915 against 200 in 1917. The per capita cost for 1916, omitting overhead, was \$1.24. In 1917, omitting overhead, which was slight, the per capita cost was \$.63. At \$2.00 per call this community had been paying nearly four times as much in doctors' bills alone as was expended in 1917 for being practically free of malaria and from the mosquito as a pest.

In four communities in Arkansas, physicians' calls were reduced from 3,394 (the average for the two previous years) to 1,120 in 1919—a reduction of sixty-seven per cent. The per capita cost of this work, with overhead expense omitted, was sixty cents. In one locality in Arkansas, screening the houses alone was tried. By this means the degree of malarial control reached 70.6 per cent, while the annual per capita cost, less overhead, was \$1.75. In another locality the prophylactic use of quinin controlled 64.45 per cent of the malaria at a per capita cost of fifty-seven cents. It was found that in getting the best effects from the prophylactic use of quinin it was necessary to furnish the drug free of cost and to personally distribute it among the people. When the people had to buy it, although it was sold at cost price, reduction in the disease was not so marked. A two-year field experiment in attempting to control malaria by the prophylactic use of quinin

was carried out in a section of Bolivar County, Miss., during the years 1916-17. More than 25,000 individuals had this treatment and it was found that ten grains of quinin daily for ten days sterilized the blood of ninety per cent of the carriers to whom it was administered. It was found that personal contact with the people is necessary to induce large numbers to take the drug regularly and for a period sufficiently long to sterilize their blood. Mass education or trying to teach and con-

REDUCTION IN MALARIA MORTALITY

Number of Physicians Calls for Malaria in
Crossett, Arkansas



Rockefeller Foundation
Annual Report 1917 Page 190.

Fig. 44.

vince the people by public lectures proved less effective than house to house visitation.

In killing mosquitoes within the house a method first proposed by Austen in 1901 and later employed by Le Prince on the Canal Zone was tried. The inside walls of the cabins are whitewashed and a black band forming a dado about three inches broad is drawn around the wall between three and four feet from the floor. When mosquitoes enter the house they alight on the dark band. This gives the children an opportunity to kill them. In the negro cabins of the South this method has been necessarily modi-

fied. There are so many dark crevices in the walls between the logs that the mosquitos prefer these to the artificial dado and thus escape destruction. The method has, therefore, been improved upon by covering the inside of the walls with white paper, which gives to the surface a relatively smooth character and leaves the dado as the most

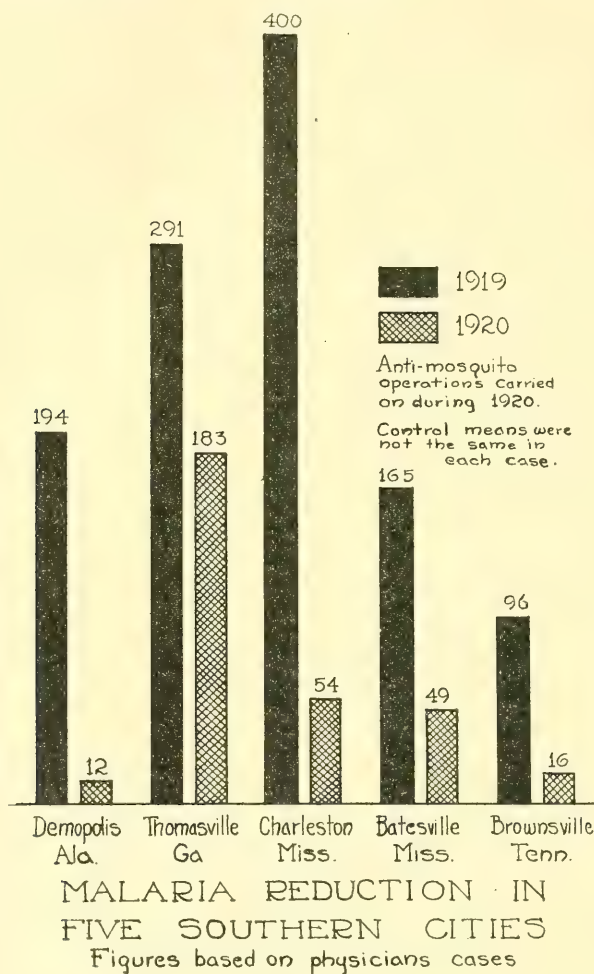


Fig. 45.

attractive place for the recently arrived insect. How long a smooth surface can be maintained by this method in the average negro cabin remains to be demonstrated. We are inclined to predict that some further modification will be found desirable. This paragraph was written in 1920. Further experience has led to the abandonment of this procedure.

In some localities drainage and other methods of destroying or rendering inoperative breeding-places have been tried. In a small section of a Mississippi county 18.1 per cent of the people had malaria in 1918, while under drainage this percentage was reduced to 5.5 in 1919. The cost of drainage varies within wide limits according to local conditions. In Hinds County, Miss., the cost per capita by this method was in 1919, \$2.60. Ponds were cleared of their vegetable growth and stocked with top minnows. These fish have proved especially effective in ponds which have been provided and maintained for the purpose of furnishing water for horses and cattle.

During the present year (1922) a new experiment is being made in the Delta of the Mississippi. Engineers state that the drainage of this region would cost so much that it cannot possibly be done. The region is low, level, intersected with a patch-work of swamps and bayous, in all of which anopheles breed abundantly. The houses of the laborers are scattered over this region, being located generally on the banks of bayous. It is proposed to concentrate the houses on a given plantation at a few points selected with reference to control of breeding-places, with the hope that in these villages protective measures which are feasible can be made operative. The field hands will spend their nights in these protected villages and will go out to their work in the malarious districts during the daytime. A similar plan has been in operation in certain sections of Italy for hundreds of years. The peasants live in some village located high up on a hill and go out to work during the daytime in the malarial lowlands; indeed, it long ago became a habit of those who live in the Roman Campagna to build scaffolds upon which they sleep at night. Anopheles do not fly high and even in highly malarious countries those who sleep in the second story are less likely to be infected than those who pass the night below.

Malaria Reduction in U. S. Army Experience.—Formerly a scourge of armies, as has been mentioned, malaria has by control measures been reduced to almost negligible proportions. During 1917 and 1918 there were 14,087 hospital admissions for malaria in the U. S. Army. This was a rate of less than 3.0 per 1000. If malaria had prevailed to the same extent as during 1861-62 of the Civil War, there would have been 1,526,572 cases, or 108 times as much. Similarly, if it had prevailed as it did during 1898-99 of the Spanish War there would have been 1,906,066 cases, or 135 times the amount of 1917-18.

The admission rate for the entire army in 1906 was 1274. This has declined to a minimum figure of 2.30 for 1919. In 1920 the rate rose to 8.45. In this year the rate for white troops in the United States was 7.54; in Europe, 1.38; in Philippine Islands, 8.37; in Hawaii, 0.80; in Panama, 55.13; in China, 3.24. The total rate for all white troops

MALARIA MORBIDITY IN U.S. ARMY

Admissions to hospital
that might have occurred
in 1917-18 with malaria
as prevalent as in —

1861-62

1,526,572

1898-99

1,906,066

Admissions that did occur in—

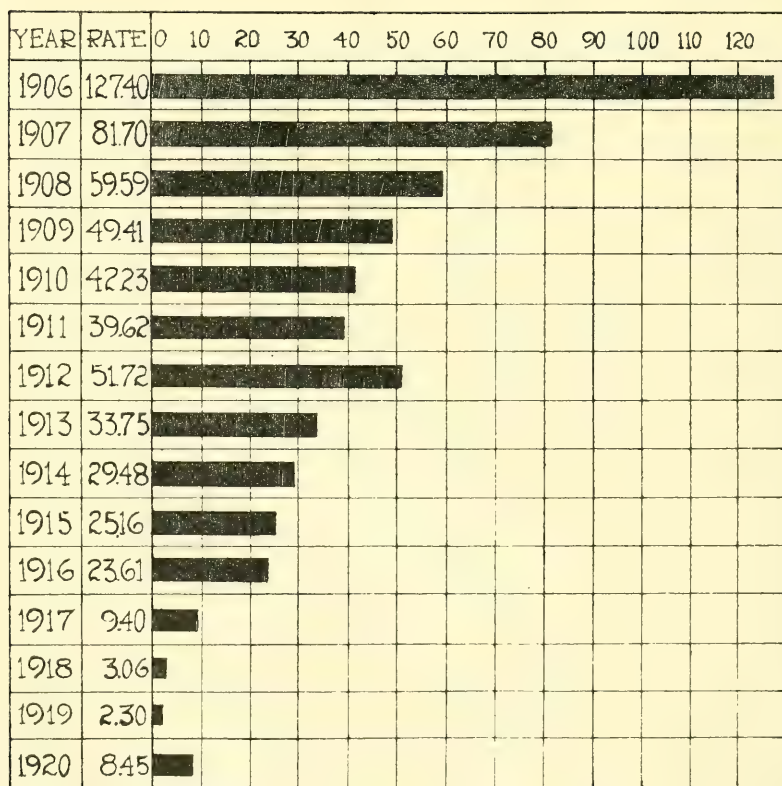
1917-18

14,087

Fig. 46.

MALARIA MORTALITY IN U.S. ARMY

Officers and American and native troops
Rate per 1000 of Admissions to Hospital for Malaria Fever



Report of Surgeon General U.S. Army.

Fig. 47.

was 7.92; for colored, 11.06; for Porto Ricans, 24.79; and for Filipino native troops, 26.32. The reduction from year to year has been carried out by increasing attention to antimalarial measures, including the draining of swamp areas and the oiling of areas that could not be drained. The Public Health Service carried on this work in the extra cantonment zones. The cutting down on this work following the close of the war undoubtedly accounts for the increase apparent in 1920.

During the period when camps and cantonments were open in 1917 and 1918 malaria was confined largely to a few of the southern camps. During the five summer months from April to August, 1918, inclusive, the four highest case rates were 40.4 for Camp Beauregard (Louisiana), 24.6 for Camp Shelby (Mississippi), 23.5 for Camp Pike (Arkansas), 12.8 for Camp Sevier (South Carolina). Contrasted with the above rates were 0.6 for Cody (New Mexico) and 0.5 each for Upton (New York), Custer (Michigan) and Funston (Kansas).

During the four autumn months, September to December inclusive Camp Beauregard again headed the list with an admission rate of 42.8. Las Casas in Porto Rico was second with a rate of 31.3. Next in order came Wheeler (Georgia) 16.1, Sevier (South Carolina) 12.1 and Eustis (Virginia) 10.7. Most of the malaria occurred in men who contracted the disease prior to entering camp. The malaria control measures about the camps were so well handled that little, if any malaria was contracted in the camps. Camp Meade reported that of the 24 cases of malaria in July, 1918, all occurred in recent arrivals and were plainly recurrences of old infections. Camp Sevier reported that no cases of malaria developed except in men coming from malarious districts.

Bibliography

- BOYCE, R.: *Mosquito or Man*, Ed. 2, London, 1910, John Murray.
- CELLI, A.: Trans. from the Sec. Italian Ed. by Eyre, Longmans, Green & Company, London, 1900.
- CRAIG, C. F.: *The Malarial Fevers, Haemoglobinuric Fever and the Blood Protozoa of Man*, New York, 1909.
- CRAIG, C. F.: *Prophylaxis of Malaria with Special Reference to the Military Service*, Government Printing Office, 1914.
- HENSON, G. E.: *Malaria: Etiology, Pathology, Diagnosis, Prophylaxis and Treatment*, St. Louis, 1913, C. V. Mosby Company.
- HOWARD, DYAR, AND KNAB: *The Mosquitoes of North and Central America and the West Indies*, Carnegie Institution of Washington, 1912.
- LUDLOW, C. S.: *Disease-Bearing Mosquitoes of North and Central America, the West Indies and the Philippine Islands*, Government Printing Office, 1914.
- ROSS, R.: *The Prevention of Malaria*, New York, 1910, E. P. Dutton & Company.
- WATSON, M.: *The Prevention of Malaria in the Federated Malay States*, Ed. 2, London, 1921.

CHAPTER XXII

YELLOW FEVER

Definition.—Yellow fever is an acute, infectious, febrile disease, highly fatal, and until recently, endemic in the West Indies and in certain localities in Central and South America. The virus, which has been identified recently by Noguchi under the name of *Leptospira icteroides*, is distributed from man to man by a species of mosquito, *Stegomyia calopus*. From time to time in the past this disease has been transported from the endemic area to diverse parts of the tropical and temperate zones, and when such regions are infested by the *stegomyia* local epidemics have resulted. The disease is characterized by sudden onset, with rapid elevation of temperature, with or without chills, accompanied by marked pain in the muscles, especially in the back. As a rule, there is nausea and vomiting. The ejected matter is dark brown or black, constituting the characteristic black vomit (*vomito negro*). With the development of the symptoms the skin takes on a peculiar coppery tint, which gives to the disease its popular name.

History.—There has been some discussion as to whether yellow fever existed in the Eastern Hemisphere before the time of Columbus. We believe that if yellow fever did exist in the Eastern Hemisphere prior to the time mentioned, it must have been confined to remote parts of Africa. It seems quite certain that it never appeared about the Mediterranean Coast. A disease with such characteristic symptoms and so deadly, certainly would have been observed and described had it come under the observation of the more intelligent physicians of that region of the earth at any time. There can be no doubt about the existence of malaria in ancient Greece or in Italy before the Christian era, nor is there any doubt about the appearance of the plague in the Mediterranean region. The manifestations of yellow fever are quite as characteristic as those of either malaria or the plague, and we feel we are justified in concluding that yellow fever was confined to the Western Hemisphere before connection between the two hemispheres was established by Columbus and his sailors. There is a tradition that Columbus himself suffered from this disease somewhere on the southern coast of Cuba about the year 1495, but this is tradition and we have no positive information bearing on the subject. The first unquestionable description of the disease was that of du Tertre, who observed it in Guadaloupe in 1635, and from that time on yellow fever is described as appearing in severe epidemic form, certainly in the West Indies and in certain parts of

Central America. There was a quarantine put upon this disease at European ports, beginning early in the eighteenth century and extending up to 1790. The French Revolution and the Napoleonic Wars put an end to the effectiveness of this quarantine and during the period from 1791 to 1815 yellow fever made frequent excursions not only to Europe, but to remote parts of North and South America. According to Béren-ger-Féraud, who wrote in 1891, the most intense endemic area of this disease during the century preceding the writing was on the Atlantic Coast of Mexico and Central America. During the same time it was

THE RAVAGES OF EPIDEMIC DISEASE IN NEW ORLEANS, DURING THE LAST CENTURY

1820-1919

CRUDE DEATH RATE PER 1000 OF POPULATION

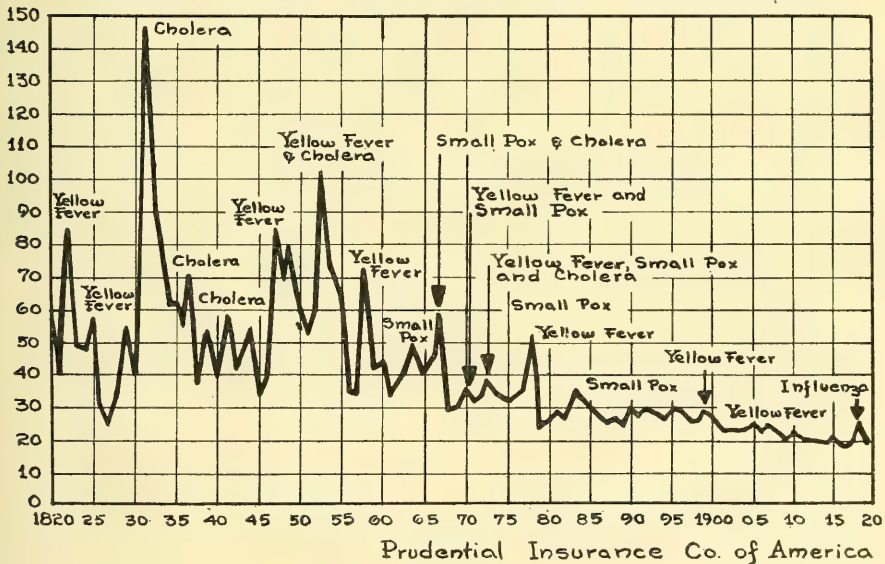


Fig. 48.

endemic in the Greater Antilles, including the Islands of Cuba, Jamaica, San Domingo, and Porto Rico; and somewhat less prevalent in the Smaller Antilles, including Martinique, Antigua, Guadeloupe, and other islands. It is probably safe to say that, at least from the time of Columbus down to the close of the nineteenth century, there were endemic areas of this disease in the regions just mentioned. There are those who believe that the endemic area should include the coast of Brazil, the western coast of South America, and certain sections of the Atlantic Coast of Africa. There are others who hold that this disease was not endemic in Brazil, although repeatedly carried to that country, before

1850. From the last-mentioned date up to the end of the nineteenth century yellow fever undoubtedly occurred frequently on the Atlantic Coast of Brazil, especially at Rio. The author just referred to thinks that the disease cannot be said to have become endemic in either Brazil or on the western coast of Africa, although he admits that it was frequently imported into these regions.

During the latter part of the eighteenth and during the greater part of the nineteenth centuries yellow fever made frequent invasions of North America, extending at one time as far north as Montreal in Canada and Portsmouth, N. H. During this time yellow fever found a foothold in the United States about ninety times. Among the larger cities visited were New York, Philadelphia, Baltimore, Charleston, and New Orleans. The epidemic of 1793 killed ten per cent of the population of Philadelphia; that of 1853 destroyed 8,000 in New Orleans.

The United States Mortality Statistics contain a record of 464 deaths from yellow fever in the registration area from 1900 to 1919. In the single year 1905, 438 deaths occurred, 434 of these in New Orleans. Among males there were 304 deaths, females 130. Most of the deaths were among white people, only 19 occurring among the colored. One death occurred in Maine in 1916 and one in Louisiana in 1919. The deaths by years in the registration area were as shown in Table XXXIV.

TABLE XXXIV

YEAR	DEATHS	YEAR	DEATHS
1900	1	1910	0
1901	2	1911	0
1902	1	1912	0
1903	17	1913	0
1904	0	1914	0
1905	438	1915	0
1906	0	1916	1
1907	1	1917	0
1908	2	1918	0
1909	0	1919	1

The financial loss to the United States from the one epidemic of 1878, in which Memphis was visited, is estimated as having amounted to \$15,335,000. Occasionally the disease found its resting place, where it spread locally, in some relatively small interior town; such was the outbreak at Decatur, Ala., in 1888. It was soon observed that when it found a foothold in the United States, sanitation in the ordinary sense had no effect and that it disappeared with the oncoming of frost. It never was known to hibernate within the limits of this country. Rogers, writing in 1911, says:

“The extreme limits yet invaded are Quebec, 46° 56' north latitude, and Montevideo 34° 54' south latitude, in the Western Hemisphere; Swansea, 51° 37' north latitude, and St. Paul du Loanda, in the Congo State, 9° south latitude, on the eastern side of the Atlantic. Near the southern limits the disease has proved to be very virulent, but at most northern places attacked, it was distinctly attenuated in character, while they are situated on the isothermic line of 16° C. or 60° F. mean temperature at the hottest season of the year. Fortunately, outbreaks are very rare in these higher latitudes, although serious ones have occurred in Spain and Portugal, especially in the first two decades of the eighteenth century, extending to Leghorn in Italy in 1804, and milder ones in the same areas in 1870 and 1878. In 1861 St. Nazaire in France was attacked, while in 1865 the disease was imported into Swansea from Cuba. In 1878 the disease overran the United States, no less than 132 towns being infected, and about 16,000 persons carried off; but since that date only the southern towns have occasionally been attacked, New Orleans having suffered within the last few years. In 1854 Peru was severely attacked, which is of interest as showing that countries bordering on the Pacific Ocean are not exempt, so that when the Panama Canal is open great precautions will be necessary to prevent the tropical shores of the Pacific—and possibly even the Indian Ocean—being invaded. There appears to be no reason why the importation of the infection into the doubtless very susceptible inhabitants of those areas should not be followed by appalling epidemics, far exceeding anything yet known in the endemic areas of the disease, where so many of the inhabitants are immune, while such epidemics might be followed by the permanent settling of the disease in an endemic form in parts of the world where the temperature and other conditions are suitable.”

It may be of epidemiologic interest to go somewhat minutely into the outbreaks of this disease in Europe. The first unquestionable appearance of the disease in Portugal occurred in 1723. We have been unable to find any estimate of the population of Lisbon at that time, but it is evident that the disease spread widely among the inhabitants and that the death rate was great. In 1850 a ship, The Edward IV, arrived at Oporto from Brazilian ports infected with yellow fever. The disease was first observed among the custom house officers but did not spread widely through the city. A year later from two to three ships carried the disease to Oporto and at this time it became widespread. In 1856-1857 a severe epidemic, killing more than 5,000 people, occurred in Portugal, from whence it was transferred to the Azores. Quite naturally, at that time Spain was in more danger of infection from the West Indies and South America than any other country, and epidemics occurred in Cadiz and other cities almost annually during the first half of the eighteenth century. The epidemic of 1741 is said to have caused 10,000 deaths. Then for quite half a century yellow fever was unknown in Spain. Suddenly it again appeared in 1800, and in that year destroyed 17,500 persons. From 1800 to 1821 yellow fever appeared almost annually in Spain, involving ports not only on the Atlantic Coast, but those on the Mediterranean Sea. There were light epidemics in 1823 and 1829. Then there was an interval of immunity

extending to 1870. The latest known occurrence of the disease in Spain was in 1879, when it invaded Madrid but did not prevail widely.

There is no authentic history of yellow fever in France until 1802, when several cases occurred, both at Brest and at Marseilles. It was introduced into St. Nazaire in 1861 by a sailing vessel from Havana and it spread to seven other vessels lying in port. There have been five outbreaks of yellow fever in the British Isles, these occurring between 1817 and 1865. The first appearance of the disease in Italy was at Leghorn in 1804, where it prevailed for four months, causing, according to one author 700 deaths, and according to another, 1,900. Yellow fever was reported in the Province of Naples in 1883, but there seems to have been some doubt about the correctness of the diagnosis. The most eastern appearance of yellow fever, certainly so far as the Mediterranean is concerned, was reported in Trieste in 1894. It is reported that the contagion was brought from Brazil by two sailors who landed from a pest-ship at Genoa and went by land to Trieste. On account of the short incubation period of the disease this report must be received with reservation. We have given these brief statements to show how far from its endemic centers yellow fever has been carried, especially in the days when sailing vessels were so largely employed in trade. At that time it was believed that the virus was carried in infected clothing, baggage, and cargoes. It would be impossible to estimate the total financial cost of combating this disease by quarantine and disinfection. When General Wood was made military governor of Santiago in 1898 he set to work immediately to clean the city, and indeed the whole province. He succeeded in making Santiago an exceptionally clean place, certainly compared with other cities in Cuba, but he soon observed that his efforts were futile so far as the eradication of yellow fever was concerned. Our old methods of combating this disease were costly and at the same time ineffectual.

Finlay, of Havana, was the first, so far as we know, to suggest the transmission of yellow fever through the agency of a mosquito. In 1881 he read a paper, entitled, "The Mosquito Hypothetically Considered as the Agent of Transmission of Yellow Fever" before the Royal Academy of Havana, from which we make the following extract:

"Three conditions are necessary in order that yellow fever may be propagated: (1) The existence of a yellow fever patient into whose capillaries the mosquito is able to drive its sting and to impregnate it with the virulent particles, at an appropriate stage of the disease. (2) That the life of the mosquito may be spared after its bite upon the patient until it has a chance of biting the person in whom the disease is to be reproduced. (3) The coincidence that some of the persons whom the same mosquito happens to bite thereafter shall be susceptible of contracting the disease."

Finlay not only suspected the mosquito, but he hit upon exactly that

species which was afterwards shown to be responsible for the transmission of the disease. He made a number of experiments involving more than 100 individuals. He did succeed in producing three cases of mild fever, but inasmuch as his results were not uniform he at no time claimed that he had thoroughly proved his case. As we now know, there are certain conditions which must be complied with in securing positive results and these were not known at that time by Finlay or any one else. However, this indefatigable worker continued his researches and never altogether lost faith in his belief, and lived to finally see the problem solved by others along the lines he had laid down. Finlay should not be regarded as a mere dreamer who had been fortunate in his dreams, but he was a man who proceeded at all times along scientific lines and that he failed to completely demonstrate the correctness of his theory was no fault of his.

Investigations as to the transmission of yellow fever were diverted from the right course in 1885 by Freire, of Rio de Janeiro, who claimed that he had found the specific cause in an organism, which he named *Cryptococcus xanthogenicus*. In 1887 Sternberg, of the U. S. Army, was sent to Rio to investigate and report upon the work of Freire. Sternberg did laborious and most excellent work, but his results were negative. He found that the so-called "specific cause" offered by Freire was nothing more or less than the common *Staphylococcus pyogenes albus*. Sternberg continued his work in Havana and it may be said that, while he failed to find the specific cause of yellow fever, he made it quite certain that no bacterium found in the body after death from this disease could be its cause; in other words, Sternberg did in a most thorough manner a necessary piece of research which again turned attention to the necessity for more thorough investigation of the claims of Finlay. In 1897 the scientific world was again stirred by the announcement by an Italian bacteriologist, Sanarelli by name, that he had succeeded in finding the true cause of yellow fever and that it was a bacterium, to which he gave the name *Bacillus icteroides*. However, it was soon shown that this was nothing more or less than a bacillus which Sternberg had obtained ten years before and had carried in his protocol as *Bacillus X*; in fact, the bacillus of Sanarelli turned out to be a variety of the hog cholera bacillus and only a secondary invader in yellow fever.

About this time Carter, of the U. S. Public Health Service, studying yellow fever epidemics in the southern states, made a vital observation. He noticed that when a first case of yellow fever developed in a community a period of from 15 to 20 days elapsed before secondary cases occurred. Holding to the mosquito theory, this observation made by Carter could mean only one thing—that the mosquito after biting a

yellow fever patient must carry the parasite from 10 to 15 days in its body before it could transmit effectively the parasite to another individual; in other words, it indicated that the virus of yellow fever, whatever it may be, passes through a life-cycle in the body of a mosquito and to do this requires from 10 to 15 days, since as was well known the period of incubation in yellow fever is something less than five days. This offers a ready explanation of why Finlay in his large number of experiments had obtained no uniform results. If a *stegomyia* bites a yellow fever patient at a period when the virus is in his blood this mosquito cannot transmit the disease until the parasite has undergone a definite development in the body of the insect.

In 1897, Smith, of the U. S. Public Health Service, then in charge of the National Quarantine Station on Ship Island in the Gulf of Mexico, treated some 30 cases of yellow fever brought to the station by infected vessels and at the same time cared for other patients, while the only precaution against the spread of the disease consisted in screening all windows and doors. No case of yellow fever developed at the station.

In 1900, with Cuba under military rule, Surgeon General Sternberg, appointed a Yellow Fever Commission, consisting of Reed, Carroll, Lazear, and Agramonte, to study the transmission of yellow fever. This Commission established an experimental station in the open about a mile from Quemados, the military post. Two mosquito-proof houses were built. Bedding, blankets, soiled sheets, and pillow cases from beds on which yellow fever patients had lain sick and had died, were brought from Havana and used for the bedding supplied in one of these houses. Young soldiers, nonimmunes, slept in this house on the articles mentioned, many of which were badly soiled with vomit and other excretions of yellow fever patients. The beds in this house were occupied by these men for periods of from 20 to 21 days. Then the men were taken to quarantine and kept under observation for at least five days. When one batch left the house another occupied it. In all, this house was occupied for 63 days by nonimmunes, who lived day and night in the midst of soiled clothing, bedding, etc. However, they were protected against mosquitoes. No one developed this or any other disease but all remained in perfect health. This demonstrated that yellow fever is not conveyed by fomites and showed that all the time, work, and money which had been bestowed upon the disinfection of clothing, bedding, and cargo, in order to protect our cities from yellow fever had been in vain; in other words, the century-old idea that yellow fever is acquired by contact, either directly or indirectly, was exploded.

The second house contained two rooms which were separated by a wire screen partition. All the furnishings that went into this house were thoroughly disinfected or were new and perfectly clean. Non-

immunes were placed in both rooms. Into one, mosquitoes which had been reared from the larvae and which had been permitted to bite yellow fever patients from 10 to 15 days previously, were loosened. Thus the Commission provided a two-room house with only a wire screen partition between the rooms. There were nonimmunes in both rooms. All mosquitoes were excluded from one room, while into the other, mosquitoes laden with the blood of yellow fever patients were admitted. All the men in the room from which mosquitoes were excluded remained well; fifty per cent of those in the room containing infected mosquitoes developed yellow fever.

On August 27, 1900, one of the Commission, Carroll, was submitted to the bite of an infected mosquito. We shall give Carroll's account of his own case in his own words:

"The insect, which had been hatched and reared in the laboratory, had been caused to feed upon four cases of yellow fever, two of them severe and two mild. The first patient, a severe case, was bitten twelve days before; the second, third, and fourth patients, had been bitten six, four, and two days previously, and their attacks were in character, mild, severe, and mild, respectively. In writing to Dr. Reed on the night after the incident I remarked jokingly that if there were anything in the mosquito theory I should have a good dose; and so it happened. After having slight premonitory symptoms for two days I was taken sick on August 31, and on September 1, I was carried to the yellow fever camp. My life was in the balance for three days, and my chart shows that on the fifth, sixth, and seventh days my urine contained eight-tenths and nine-tenths of moist albumen. The tests were made by Dr. Lazear. I mention this particularly because the results obtained in this case do not agree with the twentieth conclusion of Marchoux, Salimbeni, and Simond, that the longer the interval that elapses after infection of the mosquito the more dangerous it becomes. Twelve days, the period above cited, is the shortest time in which the mosquito has been proved to be capable of conveying the infection. It is my opinion that the susceptibility of the individual bitten is a much more potent factor in determining the severity of the attack than the duration of the infection in the mosquito, or the number of mosquitoes applied. On the day that I was taken sick, August 31, 1900, Dr. Lazear applied the same mosquito, with three others, to another individual who suffered a comparatively mild attack, and was well before I left my bed. Thus it happened that I was the first person to whom the mosquito was proved to convey the disease. On the eighteenth day of September, five days after I was permitted to leave my bed, Dr. Lazear was stricken and died in convulsions just one week later, after several days of delirium with black vomit. Such is yellow fever."

Lazear had submitted to an experimental bite without any effect, but a short time afterwards a mosquito settled upon his hand while he was collecting blood from yellow fever patients and he allowed it to take its fill. After the usual period of incubation he developed yellow fever in its most virulent form, and, as has been said, died within a week.

We make the following quotation from Reed's report:

"It was now proposed to attempt the infection of nonimmune individuals in three different ways, namely, first, by the bites of mosquitoes which had previously bitten

cases of yellow fever; second, by the injection of blood taken during the early stages from the general circulation of those suffering the disease; and third, by exposure to the most intimate contact with fomites. For this purpose, in addition to the seven tents provided for the quartering of the detachment, two frame buildings, each 14 by 20 feet in size, were constructed. These buildings, having a capacity of 2,800 feet, were exactly similar, except that one of them, known as the 'infected mosquito building,' was divided near the middle by a permanent wire screen partition and had good ventilation; while the other, designated as the 'infected clothing building,' was purposely so constructed as to exclude anything like efficient ventilation. These houses were placed on opposite sides of a small valley, about 80 yards apart, and each 75 yards distant from the camp proper. Both houses were provided with wire screened windows and double wire screen doors, so that mosquitoes could be kept within or without the buildings as the experimenters might desire."

Reed and his coworkers demonstrated that blood taken from yellow fever patients during the first three days of the disease and injected into nonimmunes produces the disease. Furthermore, it was found that such blood after filtration through porcelain still causes the disease; in other words, the virus, whatever it may be, is filtrable.

The species of mosquito with which Reed and his coworkers made their experiments was at that time believed to belong to the genus *Culex*. In his final report on the etiology of yellow fever, Reed sums up his work as follows:

"(1) The mosquito, *C. fasciatus*, serves as the intermediate host for the parasite of yellow fever. (2) Yellow fever is transmitted to nonimmune individuals by means of the bite of a mosquito that has previously fed on the blood of those sick of the disease. (3) An interval of about 12 days or more after contamination appears to be necessary before the mosquito is capable of conveying the disease. (4) The bite of the mosquito at an earlier period after contamination does not appear to offer any immunity against a subsequent attack. (5) Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease. (6) An attack of yellow fever, produced by the bite of the mosquito, offers immunity against subsequent injection of the blood of an individual suffering from the nonexperimental form of the disease. (7) The period of incubation in 13 cases of experimental yellow fever has varied from 41 hours to 5 days and 17 hours. (8) Yellow fever is not conveyed by fomites, and hence disinfection of articles of clothing, bedding, or merchandise, supposedly contaminated by contact with those sick with this disease, is unnecessary. (9) A house may be said to be infected with yellow fever only when there are present within its walls contaminated mosquitoes capable of conveying the parasite of this disease. (10) The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects. (11) While the mode of propagation of yellow fever has now been definitely determined, the specific cause of this disease remains to be discovered."

In our discussion of malaria, we have shown how the splendid discovery of Reed and his coworkers enabled Gorgas to rid Havana of this disease and later to protect the builders of the Panama Canal. The work done by Reed and his coworkers was experimentally confirmed

by Guiteras in Havana, by a Commission from the U. S. Public Health Service working at Vera Cruz, and finally by a French Commission sent from the Pasteur Institute of Paris to Brazil.

In order that we may have adequate appreciation of the value of Reed's work, we shall quote from an account of the yellow fever epidemic in Philadelphia in 1793, written by Carey:

"The consternation of the people of Philadelphia at this period was great beyond all bounds. Dismay and affright were visible in the countenance of almost every person. Of those who remained, many shut themselves in their houses and were afraid to walk the streets. . . . The corpses of the most respectable citizens, even those who did not die of the epidemic, were carried to the grave on the shafts of a chariot, the horses driven by a negro, unattended by friend or relative, and without any sort of ceremony. People hastily shifted their course at the sight of a hearse bearing remains there. Many never walked on the footpath, but went into the middle of the streets, to avoid being infected in passing by houses wherein people had died. Annunciations and funerals avoided each other in the streets and only signified their region by a loud wail. The old custom of shaking hands fell into such disuse that many shrank back with affright at even the offer of the hand. A person with weep, or any appearance of mourning, was shunned like a viper, and many valued themselves highly on the skill and address with which they got to the window of every person they met. Indeed, it is not probable that London, at the last stage of the plague, exhibited stronger marks of terror than were to be seen in Philadelphia from the twenty-fourth or twenty-fifth of August till pretty late in September. While affairs were in this deplorable stage, and the people at the lowest ebb of despair, we cannot be astonished at the frightful scenes that were enacted, which seem to indicate a total dissolution of the bonds of society in the severest and dearest connections. Who, without horror, can reflect on a husband deserting his wife, united to him, perhaps for 20 years, in the last agony—a wife unfeelingly abandoning her husband on his death-bed—or parents forsaking their only children without remorse—children ungratefully flying from their parents and resigning them to chance, without an inquiry after their health or safety—masters hurrying off their faithful servants to Bushkill, even on suspicion of the disease, and that at a time when, like Tartarus, it was open to every visitor, but never returned any—servants abandoning the tender and humane masters, who only wanted a little care to restore them to health and usefulness—who, I say, can even now think of these things without horror?"

In contrast to the above quotation, it is pleasing to know that the best physicians of Philadelphia at that time remained at their posts and administered to the needs of their patients, many of them sacrificing their lives in this service. The following is a quotation from a letter written by Benjamin Rush, then dean of the medical profession of Philadelphia:

"After the loss of my health I received letters from friends in the country, pressing me in the strongest terms to leave the city. Such a step had become impossible. My aged mother was too infirm to be removed, and I could not leave her. I was, moreover, part of a little circle of physicians who had assumed themselves in support of the new remedies. This circle would have been broken up by me, leaving the city. The weather varied the disease, and in the weakest state of our body I expected to be able, from the reports of my pupils, to assist my associates in detecting its changes

and in accommodating our remedies to them. Under these circumstances it pleased God to enable me to reply to one of the letters that urged my retreat from the city that I had resolved to stick to my principles, my practice, and my patients to the last extremity."

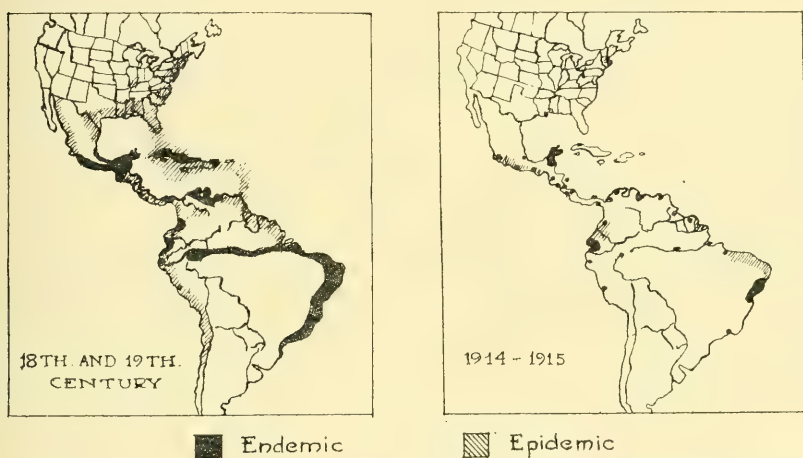
In 1903 there was an epidemic of yellow fever in Laredo, Texas, and the city of the same name in Mexico immediately across the Rio Grande. From September 25 to November 30, there were 1,050 cases of yellow fever, 691 of which were Mexicans and 359 Americans. There were 103 deaths, 8 being among Americans. The measures that had proved so effective in Havana were immediately put into operation in Laredo, with the result that the epidemic was stamped out.

An epidemic of yellow fever was recognized in New Orleans on July 12, 1905. White, of the U. S. Public Health Service, and Kohnke, of the local board of health, took charge and put into operation antimosquito measures. Although the epidemic had become widespread and the number of infected mosquitoes large, the work can certainly be called successful, since the number of deaths (460) was just a little more than one-tenth the toll paid by that city in the epidemic of 1878, although in the interval the population of the city had greatly increased.

In 1918-1919 small outbreaks of yellow fever occurred in certain Central American states—Guatemala, Nicaragua, Honduras, and Salvador. These were speedily suppressed by Gorgas and White, who were sent to these countries by the International Health Board. In November, 1918, the same agency undertook the eradication of this disease from Guayaquil, Ecuador, which had long been regarded as a hot-bed for the development of the disease. The average yearly number of cases of yellow fever in Guayaquil during the period from 1912 to 1918 inclusive was 259. The International Health Board Commission entered upon an active antimosquito campaign, involving drainage, oiling, and the screening of all water containers. In the carrying out of this work the city was divided into districts of such size as to permit a weekly house to house visitation by sanitary squads. All suspicious cases were isolated and placed within metallic screening. There has been no case of yellow fever, at least no authentic case, since April 1, 1919.

Present Endemicity of Yellow Fever.—It has long been suspected that the Gulf Coast of Mexico and Central America was the original home of this disease. It is possible that yellow fever played a part in the downfall of Mayan civilization. The writings of the earliest Spanish explorers in this region show that these people suffered from a highly fatal disease. The *Stegomyia* is abundant in these localities, which have never been free from yellow fever from the time they were first visited by the Spaniards up to the present time. According to official Mexican reports, there were in that country in 1920, 505 cases of recognized yel-

low fever, with 249 deaths, and in 1921, 115 cases, with 53 deaths. At the present time (February, 1922) the disease is still prevalent in Vera Cruz and surrounding country. With the effective work done at Guayaquil it was hoped that the western countries of South America had been freed of this disease, but within a short time it appeared in Peru and at several localities in Central America. We have recently (March, 1922) been informed through the International Health Board that during 1921 there were 15,000 cases of yellow fever, with 1,500 deaths, in Peru. Thirty-seven towns and estates in the departments of Lambayeque and Libertad were swept by the epidemic. Vigorous antimosquito measures, which are now in force throughout 600 miles of coastal territory,



~YELLOW FEVER IN THE WESTERN HEMISPHERE ENDEMIC AND EPIDEMIC AREAS.

Yellow Fever etc. by Gorgas, Carter
and Lyster. International Health Board.

Fig. 49.

have brought the disease under complete control. At present there is no known case of yellow fever in the country. Within the past two or three years, it has appeared from time to time along the eastern coast of Brazil. The commission sent by the International Health Board to the west coast of Africa in 1920 did not find yellow fever in the places visited, but was convinced that the disease exists and is distributed over a large area.

Noguchi's Researches.—In 1919, working at Guayaquil, Noguchi reported that he had found and isolated the specific cause of yellow fever, to which he has given the name *Leptospira icteroides*. Concerning this parasite, he makes the following statement:

“By the employment of methods destined to promote the growth both of aerobic and anaerobic organisms, particularly those belonging to the class of spirochetes, it was possible to obtain a pure culture of a delicate organism, the morphologic features of which place it in the genus *Leptospira*. On three occasions, that is, from three out of 11 cases of yellow fever, the organism was directly cultivated. These three strains were found to induce the characteristic symptoms and lesions when tested on guinea pigs. *Leptospira icteroides* was also obtained in pure culture from the blood of guinea pigs which succumbed to infection after being inoculated with the blood or organ emulsions from patients suffering from yellow fever. These cultures also proved to be virulent when tested on susceptible animals. The morphologic characteristics and certain biologic properties of the organism were considered in detail. It is invisible under translucent illumination and is difficult to stain by most anilin dyes. It is highly sensitive to the presence of bacteria and is rapidly destroyed in a medium in which certain other organisms are present. * * * The virulence attained by some strains was such that 0.00001 c.c. of a culture could induce typical fatal infection in guinea pigs. * * * *Leptospira icteroides* passes through the pores of Berkefeld filters V and N, and there is a possibility of its having a granular phase of life under certain conditions.”

Still more recently, Noguchi reports that he has been able to prepare an effective antitoxin. The serum of convalescents may be used, or an antitoxic serum may be prepared from horses.

The Stegomyia.—As has been stated, when Reed did his work in Cuba, the yellow fever mosquito was known as *Culex fasciatus*. Having been incriminated as the carrier of so serious a disease, this insect has been closely studied by entomologists. Theobald concluded that, on account of its scale structure, it cannot be included in the genus *Culex*; therefore, its name was changed to *Stegomyia fasciata*. Some entomologists brought objections to this name and for a while it was known to entomologists, and is still known to epidemiologists, as *Stegomyia calopus*. More exact entomologists have created still another name for the genus and to them it is now known as *Aedes calopus* (again changed to *A. Egyptus*). For the present at least, we are retaining the generic name of *stegomyia*, because this is the one more generally employed by epidemiologists. The *stegomyia* is a domestic insect and is seldom or never found at great distances from habitations. In regions where it abounds it has evidently come to regard man as its essential host; indeed, the *stegomyia* is by preference an urban rather than a rural dweller. It is found most abundantly in villages and even in large cities. Both sexes live in and about houses, where they mate, reproduce their kind and rear their young; apparently under the protection, and certainly with the help, of man. The insect has apparently adapted itself to this domestic life and it makes of itself a visible and an audible nuisance to the least possible extent. It has no song and does not warn man of its presence by claiming cousinship as do the *culex* and the *anopheles* in their frequent serenades. While it refrains from noisy demonstrations, at the same time it takes

care not to be too much in evidence to the sense of sight. Its habitual method of approach to man is from the rear. Its favorite place for feeding is neither on the face nor the hands, though it may seek either locality, but is the ankle, and when it finds this part of man's anatomy protected it crawls up under the clothing and bites the legs. It crawls into our pockets and hides under our coat lapels. While it has no song and is noiseless in its attendance, its sense of hearing or otherwise apprehending danger is keen and it flies away to its hiding place quickly when it senses danger. In the house it likes dark corners, crawls behind pictures, and even enters the closet where the clothes hang and stows itself away in the folds and seams of garments, evidently with the knowledge that these articles are sooner or later likely to be brought into contact with the source of its food. This mosquito shows a decided preference for human blood, and we are told by entomologists that blood is essential to the development of its eggs. In rare instances it seems to be true that they have been found at a distance of 500 meters from a human habitation, but this seems to be rare and when a specimen is found at so great a distance from a house it is always a question as to whether the finder has not brought it along in his pocket or in some fold or seam of his garments. Barber states that he was bitten by a female *stegomyia* near Helena, Ark., after he had left the last house rather more than a quarter of a mile behind. Barber could find no breeding-place about, and, being well aware of the fact that the insect is likely to hide under coat lapels or in pockets, he concluded that he had unconsciously brought his guest and boarder with him.

Feeding Habits.—It has been stated that even the male *stegomyia* draws blood from man. However, those who have had best opportunity to study this pest are quite convinced that, while the male apparently enjoys lapping the perspiration that may stand in drops on the skin, it is not anatomically supplied with the puncture apparatus necessary to pierce the skin and draw blood. On the other hand, the female is a blood-thirsty beast; and well she may be such, since blood seems to be necessary for the development of her eggs. Goeldi is quite convinced that, while the male likes to drink perspiration and in doing so causes some irritation, it is not able to draw blood. Virgin females have been induced, it seems, to suck blood after long fasts, but it is not their habit. However, after copulation the female seeks blood and prefers human blood. Finlay offered every inducement to females captured fresh from the pupa state to bite, but was unable to bring about this result. The same investigator found that fertilized females are greedy for blood, and this has been confirmed by many other observers. The French Commission in South America placed eight virgin females so that they had abundant opportunity to bite and found that the first one sucked blood

after a fast of 54 hours. After the fertilized female has had a copious meal she becomes sluggish, flies with difficulty, finds a retired place to alight, and rests for hours at a time with a curious and continuous movement of the hind legs. Finlay states that after a fertilized female has had a full meal of blood she may occupy from two to four days in digesting it. He induced such a mosquito to draw blood 12 times in 31 days.

The French Commission, studying the *stegomyia* in Brazil, found that this insect has a decided predilection for the blood of man, but that in the absence of opportunity to secure this food it may feed upon any warm-blooded animal. Finlay made observations on the race preference of this mosquito, as follows:

“Finally, should be taken into account the preference which mosquitoes manifest toward certain races and individuals; one notes that the least tormented race appears to be the African and the individuals most persecuted by them are those of northern races who have recently come to the tropical regions of America. It appears probable that this depends upon the thickness of the skin and upon the capillary circulation of the skin; it is to be assumed that these circumstances will affect the facility with which the female mosquito can obtain the blood which it needs to complete its life-cycle.”

The French investigators concluded that this mosquito bites both the negro and the red-skinned races, but that it prefers the white. If mosquitoes of the same age and at the same temperature are placed upon black, red, and white-skinned races, the white will be bitten most quickly. They state that the *stegomyia* shows some repugnance to the negro and that it may rest in contact with his skin for from 10 to 15 minutes before it inserts its lancet. Among whites it prefers the young and vigorous, but when hungry will feed upon the first human being with which it comes into contact.

It has been shown that the *stegomyia* prefers to draw the blood itself. If the skin be pricked with a needle so that a drop of blood stands on the surface and a mosquito be brought into contact with this it does not utilize the blood on the surface, but proceeds to draw its own supply. The U. S. Public Health Commission, studying at Vera Cruz, makes the following statement:

“The approach to attack of *stegomyia* is extremely insidious, usually approaching an individual on the shady side and without warning. The pertinacity of this mosquito in returning to its victim after it has been repeatedly driven off is almost characteristic. It has been noted repeatedly by us that females escaping while being transferred from one jar to another would almost unfailingly return after a few minutes and attempt to secure food from one of us. On one occasion a marked female was driven off five times during one forenoon; once she remained away nearly an hour, when her intended victim becoming tired of further time-keeping, finally recaptured her.”

According to Neumann, the *stegomyia* does not take kindly to birds as a source of food, but will feed promptly and abundantly upon rats.

In the West Indies the *stegomyia* is known as the "day mosquito," in contradistinction to the *C. quinquefasciatus*, which is exclusively nocturnal. Finlay believed, and apparently demonstrated, that the *stegomyia* has greater resistance to heat than the *culex*. He placed females of the two species in glass tubes and exposed them to the midday rays of the sun under identical conditions. The *culex* under this intense heat, which measured about 100° F., died within a few minutes, while the *stegomyia* remained unharmed. Durham, studying mosquitoes in Brazil, has the following to say concerning the *stegomyia*:

"It is on the wing and will bite shortly after sunrise (about 6 A. M.); again, a few have been observed biting about 8 to 9 A. M., after which there is a pause till about 11 A. M., when a few may be feeding. The time of chief activity is in the middle of the day, from about 12 to 2 P. M., they then bite freely, and are seen to copulate on the wing in numbers; another pause follows, though there may be a few about, but they do not cause trouble when one is sitting at the microscope until about half past three till about 5 P. M. After dusk or dark I have only once met with a specimen; this was a male, feeding in a sugar basin rather before 7 P. M. These statements are derived from observations whilst working in the laboratory, and during a residence for a week in the house of a gentleman, whose garden was liberally supplied with ant-guards (perforated troughs filled with water, for preventing the access of destructive 'Säuba' to the plants), each of which was full of developing larvae and pupae. Sitting in the veranda of this house it was easy to catch 50 to 80 specimens without moving from one's chair, in the early hours of the afternoon, yet after sundown, not a single individual was met with."

This observation of the diurnal activities of the *stegomyia* has been confirmed by many others. Dutton says:

"The observation of Durham and others with regard to *Stegomyia fasciata* was fully confirmed at Bathurst; these mosquitoes only bite during the day, more especially in the early part of the afternoon. None of this species was collected in mosquito nets during the night."

Howard states that he found in sleeping in hotels in the southern states that when other species of mosquitoes were not in the room he was undisturbed until the room was lighted by the rising sun; then *Aedes calopus* began to bite furiously. Carter testifies that the *stegomyia* has not been found feeding in the dark nor in strong light, but that its biting activities are determined by the degree of light rather than by the time of day. It approaches its victim on the shadow side and is especially prone to attack the ankles under the table. According to Veazie, of New Orleans, the *stegomyia* "usually flies and bites in the daytime; if a light is burning at night you will find an occasional one. It is quite cunning in selecting the dark side of a person away from the light, and especially likes persons in dark clothing; old people, as they usually sit quiet, are greatly annoyed in the daytime by them." Banks, studying this mosquito in the Philippines, makes the following state-

ment: "It is altogether a day flier, individuals seen after dark only on the very rarest occasions."

Goeldi was originally of the opinion that stegomyia bites only by day, but is convinced from recent experience that with a strong electric light it will come into the house at night and bite. Moreover, he found that females kept in captivity could be induced to bite at night. Goeldi still holds that the yellow fever mosquito is diurnal in its activities, but that hunger may drive females to prolong their hunt to unusual hours and to be guided by bright lights in houses. Biting at night is, according to this observer, an exception and occurs only in the presence of artificial light. During the evening these mosquitoes remain inside the house, hiding behind pictures, under shelves, in corners, within moldings, and elsewhere. When a brilliant light is turned on in the room they leave their resting places and may feed upon the occupants.

The French Commission, studying the stegomyia in Brazil, reports that it found this pest busiest at night. This is so contrary to the observations of all others that it has awakened quite an animated discussion. Goeldi, also studying the stegomyia in Brazil, writes as follows:

"How can the most illustrious doctors of the French Medical Commission of the Institute Pasteur in Paris wish to prove, through their faith in their full scientific responsibility, that these stegomyiae in Rio de Janeiro ont pique *pendant la nuit*, when here in Para, we, conscious of the same full responsibility, in view of our positive observations for years, must declare the nocturnal bite as an exception?"

Howard has made an analysis of the French protocol and comes to the conclusion that the stegomyia is not nocturnal in its biting habits. Howard points out that this is rather a serious matter and not altogether of academic or even of scientific importance. It determines to a marked extent the formulation of quarantine regulations. For instance, after the French Commission had published its conclusion, the U. S. Public Health Service put in force a regulation covering fruit vessels while loading in yellow fever ports, which reads as follows:

"A vessel shall not lie where her crew will be exposed to the danger of contracting yellow fever, and at ports where the vessels lie at wharfs the vessel must be moved into the stream or at least 200 meters from the wharf before sunset, and not returned to the wharf before sunrise the following day."

Howard objects to this regulation and calls attention to the fact that the return of the vessel to the wharf about or soon after sunup would furnish the most serious exposure so far as the bite of the stegomyia is concerned.

All observers agree that temperature has a marked effect upon the activity, and especially upon the appetite of the stegomyia. Reed and Carroll make the following statement:

“As regards the effect of temperature on the sting of *Stegomyia fasciata*, the results of a number of observations made by us show that this mosquito will bite at temperatures of 62° F. and above. At temperatures below this point, we have not, as yet, succeeded in inducing even very hungry females to suck blood. We may, therefore, say that observations thus far made appear to show that *Stegomyia fasciata*, while not breeding at temperatures below 68° F., will still bite at a temperature as low as 62° F., but probably not at lower temperatures. If this insect is concerned in the propagation of yellow fever, it is now quite apparent why an epidemic of this disease should fall to a low ebb in the City of New Orleans during the month of November, with a mean temperature of 61.8° F., and practically ceased in December, with a mean temperature of 55.3° F. A careful study of the charts herewith submitted, showing monthly mean temperatures of the cities of Havana and New Orleans and Havana and Rio de Janeiro, together with the relative monthly mortality from yellow fever in these cities, will prove of interest, we think as showing better than laboratory observation the general effect of temperature upon the breeding and biting of *Stegomyia fasciata*. In the light of recent researches, we can now understand that while yellow fever can, and does, prevail during the entire year in Havana and Rio de Janeiro—although at a comparatively low ebb during the winter months—it cannot propagate itself in New Orleans from December to May.”

The French investigators found this mosquito highly susceptible to temperature. Their findings agree very closely with those of Reed and Carroll. If the temperature goes below 61° F. this insect becomes sluggish and will not feed. Below 57° F. it becomes torpid, flies with difficulty and no longer stands firmly upon its legs. It will bite promptly between 72° F. and 77° F., but it is most vigorous and feeds most greedily when the temperature runs in the eighties.

As has been stated, the female *stegomyia* cannot transmit yellow fever until 12 days after it has bitten a yellow fever patient. Moreover, the patient must be bitten during the first three days of his illness in order that the mosquito may become the bearer of the disease. The successful transmission of yellow fever from one individual to another through the mosquito is dependent upon these conditions. A very important question arises in this connection, and that is, how long does the adult mosquito live and how long does the infected mosquito carry its infection and remain able to transmit it to man? Reed and Carroll demonstrated that mosquitoes may infect nonimmunes at any time between 12 and 57 days after biting a yellow fever patient during the first three days of his illness. This means that the mosquito becomes dangerous on the twelfth day and that it remains dangerous at least up to 57 days. How much longer the infected mosquito carries and possesses the capability of transmitting the parasite has not been determined. The French investigators kept female *stegomyia* alive 106 days. Guiteras, in Havana, kept one infected female alive for 154 days. So far as we have been able to find, this is the longest time that this mosquito has been known to live. It is a matter of observation that the female lives longer than

the male and that the former will live longer if fed exclusively upon sweet substances and not allowed to draw blood. Without blood the female stegomyia does not deposit eggs, and it seems that when she is unable to continue her species she is permitted a longer individual life. Likewise, the male, although on the whole shorter lived than the female, lives longer when he is not permitted to contribute to the continuance of his kind by copulation with the female.

Flight.—Being a domestic animal, the stegomyia does not wander abroad through long distances but clings to its home rather tenaciously. Notwithstanding these facts, the stegomyia is apparently strong on the wing and may withstand successfully air currents which carry other species with them or force them to hiding places in the foliage. Practically, the chief interest concerning the length of flight of the stegomyia lies in the question of the transmission of yellow fever from the shore to ships. On this point Carter sums up as follows:

“Although direct observations on this problem are few, yet there are certain indirect ones, bearing, however, entirely on the aerial conveyance of the stegomyia infected with yellow fever. It is notorious that yellow fever is usually conveyed but a short ways aerially, ‘across the street,’ or more often to the ‘house in the rear,’ which is about as far as it was expected to be thus conveyed. This represents the maximum distance of about 75 yards. The two longest distances recorded in recent times of aerial conveyance, one of 225 meters and one of 76 fathoms—456 feet—are entirely exceptional. So much for the distance which the infected stegomyia is conveyed—or rather usually conveyed—aerially. On the other hand it is known that vessels moored in certain districts of the Havana Harbor did not develop yellow fever aboard, except in those who had been ashore, or unless they lay close to other vessels which were infected. This experiment has been made on so large a scale—with so many vessels and for so many years—that we must accept as a fact that an infected stegomyia was not conveyed aerially from the Havana shore to those vessels, or, allowing for errors, was very rarely so conveyed. This distance which had been found safe was something over 200 fathoms—1,200 feet. The prevailing wind was generally slightly on shore, but was not constantly blowing. Whether there is any difference in the distance to which infected or noninfected mosquitoes are conveyed, is, of course, entirely a matter of surmise. There is no apparent reason why there should be. Yet the infected stegomyiae have almost certainly become so in a house; and with their very domestic habits must be found out of doors, where they would be subject to conveyance by the wind in much smaller numbers than the uninfected insects, and consequently a lesser number of them would be conveyed aerially. Observation is needed on this subject—the distance (across water) that stegomyiae are aerially conveyed. Goldberger, very ingeniously states that, on account of its diurnal flight, the direction of the wind during the day only need be considered in estimating this factor in their aerial conveyance, and states that at Tampico he failed to find stegomyiae aboard vessels lying, for 10 or 15 days, about half a mile from a place on shore where they were abundant, while numbers of *A. albimanus* and *C. quinquefasciatus* were found. The wind was on shore during the day and calm or off shore during the night. The importance of this point is obvious, as on the coast, except when overborne by the trades, the direction of the wind is very generally different by day and night.”

It is well in this connection to again call attention to the fact, attested by many observations, that both the *stegomyia* and the *anopheles* are frequently carried on board ships by lighters, tugs, and even rowboats. Vaughan states that in 1898 he left Siboney on the southern coast of Cuba a few miles east of Santiago Harbor on the City of Santiago carrying about 300 yellow fever patients. The ship passed around the eastern end of Cuba, then turned west and proceeded to Tampa Bay, where it dropped anchor about one-half mile from Egmont Key. There were no mosquitoes on board the ship during this trip and none came on board after dropping anchor until communication with the shore was established by frequent passage of life boats. After this communication had been established it was more difficult to find rest at night in the unscreened state rooms on the ship than in the screened tents on shore.

Mating.—Union between the sexes generally takes place on the wing. The male meets the female face to face, attaches himself to her body, while she continues to fly carrying her partner. Copulation continues for only a few seconds, when the male separates himself and is ready apparently for another female. In rare instances the female alights while the two sexes are still engaged in the conjugal embrace. This, however, happens rarely and it is difficult to capture specimens while engaged in the sexual act except by smashing them between one's hands. The female, apparently bearing the burden of the male's body during the sexual act, flies slowly and while copulation continues both may be captured. Copulation takes place in the daytime and may be observed in breeding cages. The male apparently has some preference for the female which has already fed. However, feeding on the part of the female is not essential to attract the male. Mosquitoes bred in cages from the larvae and kept from the possibility of drawing blood perform the sexual act. However, no eggs are produced until the female has had a meal of blood, preferably human blood.

Breeding-Places.—It seems that when the West Indian built no cities, distributed no tin cans, tubs, or other water receptacles about his abode for the convenience of the *stegomyia*, this insect had its favorite breeding-place in tree holes. Howard states that there is a strong probability that *Aedes calopus* was originally a tree-hole breeding mosquito and that even now it will be found breeding in such receptacles, provided they are close to human habitations. There are other species of *Aedes* which at the present time breed almost exclusively, or at least very largely, in tree holes. Possibly when the Indian lived in his wigwam, a hole in a nearby tree supplied the best residence for his protégé—the *stegomyia*. Howard says:

“Originally, then, a tree-hole species, *calopus* has so perfectly adapted itself to

human civilization that it has become a true domestic form and practically dependent for its existence upon the conditions that surround human habitations. This dependency upon the human species is undoubtedly of ancient development. The preference for human blood is well demonstrated, and, as has been pointed out, the work done by several investigators seems to prove that this insect does not oviposit until after having had a meal of blood. Although Goeldi has shown oviposition after a meal of guinea pig blood he considers human blood more efficacious in bringing about ovulation. We have already demonstrated that *calopus* is essentially a town mosquito. The larvae are found practically exclusively in artificial receptacles about human habitations. It may be said that the larvae of *calopus* are never found in swamps, in pools, or in temporary puddles, even when these are in close proximity to houses."

Durham, studying the *stegomyia* at Para, makes the following statement:

"Casual water in vessels, etc., in and about houses, such as buckets, tins, washtubs, rain gutters, ant-guards (perforated troughs to protect plants in gardens, and sugar, etc., in houses), larger and deeper collections of water as casks or hogsheds full of rain water. Also in bilge water of barges, lighters, etc. Not found in sewage collections as cesspools, stable runnings, etc., although found in neighborhood in cleaner waters. Also not found in natural puddles in forests or streets."

In Havana, Reed and Carroll found this mosquito breeding most frequently in: (1) Rain-water barrels. (2) Sagging gutters. (3) Tin cans which had been used for removing excreta and which still contained a small amount of fecal matter. (4) Cesspools. (5) Tin cans placed under table legs to prevent the inroads of red ants. (6) Water at the base of leaves. (7) In one end of a horse trough in daily use.

In New Orleans, breeding-places have been found in sagging roof gutters, in water-closet tanks, in water under houses, in tanks kept in the house for the purpose of cooling wine, in the pans of water kept under the table legs to keep the ants from crawling up, in lye barrels, and in holy water fonts in the churches. Some years ago Howard called attention to the frequency with which *stegomyia* was found breeding in holy water fonts. This led to several modifications of these provisions. One substitute is a moist sponge, another consists of a faucet so regulated that the water falls into the basin only drop by drop.

Every conceivable thing in or about the house which contains water may serve as a breeding-place for the *stegomyia*. In addition to the things already mentioned, this insect has been found breeding in the small accumulations of water in the bottoms of beer bottles turned upside down and used for the borders of flower beds; in broken bottles placed on brick and stone walls; in the folded leaves of banana plants; in cisterns; in drinking pails kept in the house; in short, the *stegomyia*, being a member of the household, utilizes every water receptacle which man is kind enough to provide.

The Eggs.—The *stegomyia* deposits its eggs upon the surface or near the surface of water. They are produced after feeding upon blood in

lots which vary greatly in number. Reed and Carroll confirmed Finlay's observation that the females deposit their eggs usually within seven days after they have had a meal of blood. Sometimes this occurs within half this time. The findings of the French Commission show that the female of this species after fertilization by the male will not develop her eggs until she has fed upon blood. In one instance they placed 10 females and 15 males together in a cage on the same day they had issued from the pupae. After 48 hours three of the females were taken out and given a blood meal. One of these deposited her eggs after four days and a second after six days. After 18 days three of the females that had been fed on honey only and that had not deposited any eggs were allowed to suck blood, after which they deposited eggs within five days. The remaining females, which were not allowed to suck blood, died without depositing eggs. According to Goeldi, even unfertilized females lay eggs after being fed upon blood, but these eggs do not produce larvae. After having deposited all the eggs the female dies within 14 days. In making experiments of this kind it is necessary that the mosquitoes be bred from the larvae, because if the adults are caught one does not know whether they have fed upon blood or not. The French investigators are of the opinion that the female, in order to eliminate all the eggs in her body, must be fed several times upon blood. After having deposited her eggs, or at least one batch of them, the female will bite every 24 hours and sometimes even more frequently. It is thought that there is a reserve of spermatozoa deposited within the female and that she continues to lay eggs until this reserve has been exhausted.

Finlay says that the eggs are deposited singly or in rows of from nine to fifteen; sometimes upon the water, at other times upon adjoining objects very close to the water level, so that slight elevation of the water will float them. According to the French Commission, the eggs are laid at the edge of the water, or more frequently upon the surface of the water. According to Durham, the eggs are deposited close to the edge of the water, more rarely on the surface. At all times they are so near the surface that they are most liable to be carried to the water. Agramonte gives the following description of the method of oviposition:

"The mosquito alighted upon the water, which was in a small beaker inside the jar, with legs spread wide apart. The abdominal segments being bent forwards and downwards, she dipped her whole body until the last segment touched the surface of the water; then she rose, walked a few steps, and dipped again. This she would do repeatedly (14 to 22 times), when she would remain for a slightly longer time with the last abdominal segment touching the water, and would allow a minute white egg to issue forth upon the surface. In this way she laid at the rate of three eggs per minute, resting quietly after every sixth or eighth egg for about 30 seconds when she would resume the process."

According to Taylor, the number of eggs deposited by a single female varies from 35 to 114. Goeldi thinks that the maximum number of eggs from one female ranges between 50 and 100, but he states that on one occasion the last number was exceeded. The French Commission places the number of eggs from a single female at 144. These investigators also state that the first batch of eggs is much the largest, sometimes numbering between 70 and 95, while the succeeding batches are smaller and never number more than 30. According to Goeldi, the female with an abundant blood supply does not die until she has deposited all the eggs within her body. However, others have found on dissection of females after natural death 30 or more partly developed eggs still in the body.

The eggs are quite resistant to unfavorable external conditions. On this point Reed and Carroll state:

“The resistance of *stegomyia*’s eggs to external influences is worthy of note. Drying seems to be but little injurious to their subsequent fertility. We have found that eggs dried on filter paper, and kept for periods of from 10 to 90 days, will promptly hatch when again submerged in water. Dried eggs, brought with us from Havana, in February, were easily hatched during the month of May in Washington, furnished about sixty per cent of the usual number of larvae hatched from fresh eggs. Freezing does not destroy the fertility of the eggs. Although freezing with a mixture of salt and ice for 30 minutes has several times seemed to prevent subsequent hatching, on one occasion a batch of 155 eggs, freshly deposited, which were frozen at a temperature of -17° C., for one hour, then thawed out at room temperature and placed in the incubator at 35° C. began to hatch on the sixth day, the majority furnishing active larvae on the eighth day. In another observation, freshly deposited eggs, frozen at -17° C. for half an hour on two successive days, began to hatch on the third day as usual at incubator temperature. The resistance of *stegomyia*’s eggs to drying for a period of three months would appear to demonstrate that this genus of mosquito could survive the winter in Havana, without the presence of hibernating females. Doubtless the genus is preserved in both ways. It is probable that the same would occur in our extreme southern latitudes.”

Theobald, in England, hatched eggs two months and a half after they had arrived from Cuba. Howard states that in the majority of the species of *Aedes* the eggs do not hatch until the following year and that a percentage, with some, and we believe with many, species remains dormant until the second year. Agramonte found that eggs deposited in the lye of wood ashes, employed by laundresses in Cuba for the purpose of whitening clothes, hatched more quickly than in dirty water. According to the same observer, the egg stage is from 15 hours to 3 days. Taylor gives the duration of this stage as from 12 to 24 hours, while Goeldi gives the minimum duration as 3 days. Evidently, this depends upon external conditions, especially upon temperature. It seems probable that eggs deposited out of the water hatch more quickly when submerged than those deposited directly upon the surface of the

water. Eggs deposited upon the surface are easily submerged by disturbing the water. Some hold, however, that such submergence prevents the eggs developing even after they are brought to the surface. This depends apparently upon the temperature, and possibly upon the chemical composition of the water. Continued submergence evidently softens the egg shell and finally permits water to enter the egg, after which it will no longer develop into larva. In the normal hatching the shell splits transversely at about one-fourth the distance from the larger end, while the dead egg splits longitudinally. South American observers have tested the effect of high as well as of low temperature on the hatching of eggs. Eggs placed for five minutes in an oven with temperature ranging from 37° to 47° C., when afterwards placed in water, hatched after 48 hours. The larvae from these eggs developed in normal manner. When exposed to a temperature above 48° C. for five minutes most of the eggs failed to hatch and those that did were delayed in the process. The eggs of the stegomyia will not hatch in pure sea water, but they may develop in brackish water.

The Larvae.—The larvae of the stegomyia behave quite differently from those of the anopheles. They hang in the water almost perpendicular and when affrighted by any unusual movement they go to the bottom, where they can live for a long time without the necessity of coming to the top for air. This is a matter of considerable practical importance. When a vessel containing larvae is disturbed these insects drop to the bottom, and the greater part of the water may be dipped out without catching an individual. If the receptacle be turned up and the water poured out a large percentage of the larvae may still cling to the bottom. Stegomyia larvae are bottom feeders. Banks, studying these insects in the Philippines, says:

“They feed largely upon the sediment contained in the dregs, which may be both animal and vegetable in its character, but more frequently vegetable, as it is composed of the bits of decaying *nipa* forming roofs from which the rain water is collected. The larvae, in feeding, move forward over the bottom of the vessel, taking in the particles of food with great rapidity and rejecting tiny morsels of undesirable material in a constant stream.”

Reed and Carroll found that the larvae grow abundantly in water containing small amounts of human excreta. It has furthermore been found in breeding these insects under artificial conditions that their growth is enhanced by the addition of a small amount of feces. Temperature has a marked influence upon the development of the larvae. This point is discussed by Reed and Carroll as follows:

“We have just seen that at summer temperature the required time for a complete generation of this insect is from 11 to 18 days. We may say that at an average temperature of 75° F., or over, stegomyia multiplies abundantly. Exposure to a cooler

temperature, even for a short time daily, much retards the development of this mosquito. Thus, a batch of 51 eggs kept at 35° C., but which were placed in a cool chamber at 20° C. for two hours daily during the whole process of development, although furnishing a few larvae at the end of the third day, were not all hatched until the eleventh day. The first pupae appeared on the fourteenth day and the first mosquito on the nineteenth day; the whole process being completed in 27 days, instead of the usual 15 or 18 days. The loss of insects was about fifty per cent. Eggs kept at a temperature of 20° C. do not hatch, in our experience. Newly hatched larvae kept at this temperature develop very slowly and require about 20 days to reach the pupal stage. Mosquitoes developed under such conditions are feeble, and but few arrive at maturity. Young larvae kept at 10° C. have failed to reach the pupal stage—although some growth takes place. In one experiment more than fifty per cent were dead at the end of two weeks, and none survived the thirty-second day. Half-grown larvae and pupae exposed to a temperature of 20° C., and even as low as 10° C., continue to develop slowly, but the few insects which escape drowning have, as a rule, been of feeble strength and have refused to bite. Although the reduction of the temperature to the freezing point, or below, would not necessarily destroy the vitality of eggs of this genus of mosquito, it should be remembered that reduction of temperature to 68° F., or below, for even a few hours of the 24, will much retard the development of the generation. At a temperature less than 68° F. the eggs of this insect have ceased to hatch.”

The French investigators found that larvae of *stegomyia* placed in a solution of Marseilles soap 1-1,000 died in five minutes. In solutions containing one part of soap to 200,000 parts of water they develop normally. Larvae were found breeding in tubs in which linen had been washed. This is due to the fact that the soapy water on standing decreases in alkalinity. Although Agramonte in Havana and Jennings in Colombia found the larvae in earthen pots containing wood ashes, it must be remembered that such solutions decrease markedly in alkalinity on standing. The Yellow Fever Commission to Vera Cruz found that when water containing *stegomyia* larvae is poured upon the ground and rapidly absorbed, the insect perishes within a few hours. The larvae dried between folds of filter paper also died in a short time. However, many experiments of this kind have been made and the results reported have differed widely. This is probably due to the fact that the humidity of the air in which the experiments have been made has varied greatly. If poured upon the soil and kept moist the larvae will retain their vitality for even two weeks, possibly longer, and on the addition of more water may develop into the adult stage.

Geographical Distribution of *Stegomyia Calopus*.—There has been much discussion concerning the native habitat of this mosquito. Some of these discussions are exceedingly interesting, but the authors mix the geographical distribution of the mosquito with that of yellow fever. As is the case with malaria, the geographical distribution of the insect is much wider than that of the disease. According to Theobald, *Stegomyia calopus* has a wide range from about 38° north to the same distance south of the equator. It is found widely prevalent in Australia,

New Guinea, the Celebes, farther India, southern Japan, eastern Hindustan, the Seychelles Islands, southeastern Africa, the whole of the African west coast down to Cape Colony, Spain, and southern Italy. In the Western Hemisphere, this mosquito is found on the east coast of South America from British Guiana to the La Plata River, all through Central America down the western coast of South America, over the West Indies and the greater part of the southern United States. It should be understood that this mosquito does not hibernate in the colder portions of the territories above mentioned. Its existence during the colder season is due to the preservation of the eggs, and possibly the larvae. Since the virus is not transmitted from one generation to another through the eggs, yellow fever does not hibernate in this country. There is no instance of this kind on record. On this point, we make the following quotation from Howard:

“The foregoing consideration of the temperature conditions governing the breeding of *Aedes calopus* explains why epidemics of yellow fever have occurred on the Atlantic Coast of North America even as far north as Montreal, and may again occur, whereas no epidemic has occurred on the Pacific Coast, nor is it possible for one to occur. The summer temperature of the Atlantic Coast is for long periods at or above 80° both day and night, so that the mosquito, once carried by ship or otherwise from regions of its permanent occurrence, may breed in large numbers in our cities. It needs then only the introduction of cases of yellow fever to start an epidemic. On the Pacific Coast, on the other hand, the nights are so cold that the mosquito cannot survive. It is as regularly imported into Pacific Coast ports as into Atlantic ones. We have records of specimens taken at San Diego and San Francisco. It breeds permanently in all of the west coast Mexican seaports and must be frequently brought to the Californian coast. Yet it has never been known to appear there. This seems at first sight strange, since the mean annual temperature of southern California is much above that of eastern cities where epidemics have occurred. In San Diego and Los Angeles one sees tropical vegetation on every hand growing unprotected and severe cold is unknown. Yet the nights are cold, even in summer, and it is this condition, the low minimum night temperatures, that the freedom from *Aedes calopus*, and consequently from yellow fever epidemics, is due.”

There has been some animated discussion as to the African or American origin of this mosquito. The strongest statement for its African origin is that supplied by Goeldi, from which we make the following quotation:

“I am well acquainted with the arguments of those authors who claim that stegomyia is of American origin. They are based chiefly on the story of the voyage of Christopher Columbus. Without disputing whether the disease which killed a part of the crew of the caravels of the conquerors was indeed identical with yellow fever, does this in itself amount to a positive proof that this disease did not previously exist on the coast of Africa? Most certainly not. At most it might be objected that no historical documents exist relating to the existence of stegomyia in Africa before Columbus. Further, from the absence of any historic document about any given fact there can never be deduced the nonexistence of this fact. There are evidently many things which happened in

this sublunary world of which no human historian has left us a story and which nevertheless are most certainly true. Let's examine this question a little more closely. *Stegomyia fasciata* is, as we know, a mosquito which infests great cities, populous centers of the shore and neighboring regions. Now, I ask where were these great cities which the European invaders should have found along the Atlantic Coast from the Antilles even down to the Río de la Plata? Where are those points where the indigenous Americans were found in populous permanent residences? There were none, and this in no wise surprises us, considering the habits and customs of the Indians. The indigenous American was at all times that which he is today; endowed with the love of liberty he never had the habit or even the tendency to group and concentrate himself in really considerable collective residences. His village consisted of a few dozen houses—in most cases not even one hundred being found in a limited area. They were peasants rather than townspeople; as with ants and bees, an increase of members always produced for them as a consequence migration of groups, dismemberment—a new village was formed, half a day, a day, or two days farther up the river, farther down the river, farther in the forest, and this in turn became disintegrated in view of the restless and nomadic character of the Indian long before it could have acquired any considerable increment or dimensions. They are not properly sociable in their dwelling places; if among them the social spirit exists it merely shows itself at the time of feasts, of warlike enterprises or of great migrations, etc. During transitory and passing occasions there are indeed agglomerations of people but inchoate, ready to break up, and their camps cannot even be called temporary. The occasion over the multitude dissolves itself as by enchantment or before the breath of the wind. Now such conditions are not to the taste of *Stegomyia fasciata*.

“On the other hand, what do we find in Africa? One of the most striking ethnological characteristics of the black people is precisely the social spirit strongly developed. In the stories of all travelers we find at every moment expressions of surprise and admiration as to the grouping of houses, attaining numerical dimensions so great as to prevent a rapid census. In that country there are frequently found centers of ten, fifteen, or twenty thousand inhabitants, and yet these are barely called villages; in Africa the idea of a city is only given consideration with such centers as possess a multiple of the above figures. Here we have the condition of affairs that admirably meets that which the *stegomyia* wants and demands. It is the very best condition for its life requirements: a hot and humid climate and very large groups of human beings. All I wish to set down in brief words is that a careful comparison of the ethnological situation there and here—and this certainly constitutes a factor of the utmost importance in the matter—at once demonstrates the indubitable advantage on the side of the African origin of *Stegomyia fasciata*.

“Another series of considerations which in the highest degree tend to upset the theory, so weak in its base, of the American origin of *Stegomyia fasciata*, are opened up as soon as we weigh the results obtained by *critical examination of the partnership. Stegomyia fasciata—Culex fatigans*. In a previous essay I frequently and persistently pointed out that these two mosquitoes are inseparable companions all over the world, and I demonstrated that, one a diurnal and the other a nocturnal mosquito, have together formed a partnership admirably organized to take in daily cyclic rotation tribute from man in the tropical zone. Now it is worth while noting that the type specimen, the original which served for the first description of *Culex fatigans* by Wiedemann in 1828, came from the oriental Indies. This circumstance, if indeed by itself alone it does not amount to proof, is nevertheless of no small symptomatic importance.

“I ask this: Does this ominous partnership of *Stegomyia fasciata* and *Culex fatigans* date from yesterday? Is it perhaps an accidental result in the tropical part of the

New World? I believe that it is of a date much farther back and that we must find the locality where the pact was celebrated in some part of the Old World, and that it was not accidental but the natural consequence of an almost identity of common interests. I believe that there are good arguments indicating the Ethiopic-Indian nativity of this alliance, and the more I examine it the more it seems desirable to me that there should be a conscientious and critical investigation undertaken into the question of an eventful parallelism between the distribution and dispersion in ancient and modern times, of the black human race on the one hand, and of the two mosquito partners in their damnable offensive alliance on the other.

“It is indispensable not to lose sight of the fact that he would be ill advised who would permit himself to be impressed and influenced one-sidedly, and partially by the aspect which things present today in this field. Do you wish an example? It is not necessary to go far to find a most drastic one. Brazil today is the greatest producer of coffee and undoubtedly is the country where the greatest number of coffee trees have been planted. Now suppose for a moment that there was a complete disappearance of all historical documents proving the Asiatic origin of the coffee plant and of its introduction into Brazil via Cayenne, who would imagine that the original country of this tree was Arabia? And is it not an absolute fact that this very historical remembrance is becoming weaker every day in popular knowledge here in Brazil with the increasing interval of time separating us from the moment of introduction which nevertheless was scarcely 200 years ago?”

We have quoted the above somewhat *in extenso* because it is a strong and rather eloquent plea for the African origin of the stegomyia. However as Knab has pointed out, there are weaknesses in the arguments of Goeldi. There were rather extensive cities, at least in Central America, before the time of Columbus, as is shown by their ruins in Yucatan and neighboring provinces. Furthermore, there are evidences of extensive settlements in Goeldi's own country—Brazil, and in the neighboring countries to the west. One cannot resist the theory that in all human probability yellow fever, possibly aided by other diseases, was a factor in the deterioration of the civilization, the existence of which in Central and South America is indubitably attested by the ruins now found in these localities. Furthermore, it is within the range of possibility that the wide prevalence of yellow fever had a causative relationship to the nomadic habits of the red man at the time of his discovery by Columbus. Boyce is quite sure that both the mosquito and the disease which it transmits are indigenous to America. This author refers to one of the chroniclers of the voyage of Columbus, Oviedo, who describes the great mortality among the sailors to the newly discovered world in 1494. At the time the high death rate was attributed to the great humidity of San Domingo, and Columbus, in reporting to the King of Spain on the sickness among his men in 1498, attributed it to the peculiarities in the water and air. It appears that the first name given to this disease by the Spanish voyagers was *vomito prieto*. The word *prieto* is obsolete Spanish and more recent Portuguese. It means black and the word *negro* has been substituted for it. In 1753 Gastel-

bondo, published in Madrid his more than 40 years' experience with *vomito negro* as he had seen it at Carthagena, S. A.

There is room for discussion as to whether the original home of yellow fever is Central America, Mexico, or the West Indies. Some most distinguished investigators and students of the history of this disease are inclined to the opinion that it prevailed in Central America, including parts of Mexico, before it found its way into the West Indies. The first undoubted and unquestionable proof of its existence in Cuba dates from 1620, when it was known as "the pest of Havana."

Concerning the population of the region now known as Panama when first visited by the Spaniards, Gorgas writes that it was thickly inhabited by a mild-mannered population who lived principally by agriculture. In the records of Balboa's expeditions, he states that as he marched from town to town he easily obtained supplies and was able to procure from 500 to 1,000 porters for carrying his baggage. In every town he secured gold in such quantities that it could have been furnished only by a densely inhabited and industrious country. The Republic of Panama now covers some 31,571 square miles and it is divided into two parts near its center by the Panama Canal. The western half now contains all the population of the republic, with the exception of a few wild Indians. In Balboa's time the eastern half was the more densely populated. Columbus regarded Panama as the richest of his American discoveries and the name which he bestowed upon this country was Castilla del Oro.

Transportation by Man.—For more than 200 years the country which we now occupy was in annual danger of the importation of yellow fever from the West Indies, Central America, South America, and Mexico. Millions of dollars were spent in quarantine and in the disinfection of merchandise. Trade with the above named countries was rendered difficult and was often delayed, but nevertheless the disease was introduced into this country nearly 100 times. Ships were held at our ports for a sufficient length of time to cover what was believed to be the period of incubation. Much damage to cargoes was done and when yellow fever, notwithstanding all these precautions, found its way into one of our ports, disaster to all daily pursuits followed and was often accompanied by appalling death rates. Now we know that this disease is not transmitted by any other agency than the one species of *stegomyia*, and consequently all efforts to stay the disease and to eradicate it where it has already secured a foothold lie in the destruction of this pest.

It would be interesting, had we space, to consider some of the epidemics which have appeared in this country in the past 50 years. In 1888 there was an outbreak in the village of Decatur on the L. & N. Railroad in northern Alabama. Immediately on the appearance of

the disease at this place, Dr. Cochrane, health officer of the state, went to Decatur and attempted to inaugurate such methods as were then believed to be necessary in the control of this disease. The Mayor of the city, through the Associated Press, asked the people of the United States to send food and clothing to Decatur. The state health officer protested that this should not be done. With the arrival of the first train bearing supplies to the stricken city, hundreds of tramps, white and black, flocked to the place in order to profit by the distribution of food and clothing. The state health officer became the most unpopular man in Decatur. Notwithstanding every effort he made, the disease continued until frost, when it suddenly ceased. The people of Decatur predicted that there would be another outbreak the coming year and petitioned the President of the United States to have Decatur burned and rebuilt in anticipation of the awakening of the virus which, according to their prediction, would bring new disaster upon the locality. The state health officer, with a full knowledge of the history of every epidemic that had visited this country, opposed this petition and held that yellow fever had never been known to hibernate in this country. Fortunately, his arguments were recognized as thoroughly sound. Decatur was not burned, and there has been no case of yellow fever in that locality since. This is a single illustration of the panic into which communities fell and the reckless demands made when "yellow jack" struck a locality.

It is claimed that yellow fever is gradually but slowly progressing along the railway between Vera Cruz and the City of Mexico; that it has climbed to higher and higher altitudes where it has found suitable local conditions for the multiplication of the mosquito and the spread of the disease. On this point a commission from the U. S. Public Health Service, working in the neighborhood of Vera Cruz in 1905, wrote as follows:

"This mosquito is widely distributed, probably more so than any other species, being found throughout the tropical world and well up in the temperate zone. At one time it was supposed to be a coast mosquito, but now it is found to have spread along the commercial lines of communication to cities in the interior that furnish receptacles for breeding-places. Its acclimation to the altitudes is gradual as may be illustrated by the following example: About 28 years ago a railroad was constructed connecting Vera Cruz with the City of Mexico. Some years later a competing line was built between these cities, but going through a different part of the country. Along the line of the Mexican railroad yellow fever was unknown in the interior. During the construction of the railroad the disease prevailed among employes until the road reached the foothills; it then disappeared. About nine years ago yellow fever appeared in Cordova at about an altitude of 3,000 feet, and has since been epidemic. Three years ago yellow fever appeared at Orizaba and this year (1902) there was a severe epidemic in that city. Since the construction of the railroad many cases of the disease had been received during sickness and convalescence, and many cases have developed among

strangers going through Vera Cruz to that city without the disease in any way affecting the general health of the community, until three years ago.

"In the second instance, along the line of the Interoceanic Railroad we know by actual observation that the *Stegomyia fasciata* has been ascending from station to station until it has now reached Carasal at an altitude of about 3,000 feet. Synchronously, with the ascent of this mosquito, yellow fever became epidemic in this place. El Palmar, the next station above Carasal, about eight miles distant, does not harbor any of these insects at the present time, and although some cases were sent there from the latter station this year, there was no spread of the infection. Jalapa, a city of about 35,000 inhabitants, at an altitude of about 4,500 feet and about 20 miles above Carasal does not harbor the *Stegomyia fasciata*, and though cases have been sent to that place for years from Vera Cruz and intermediate stations, there has never been any spread of the disease. It will be seen in these instances that the ascent of yellow fever and the advent of the *Stegomyia fasciata* have gone hand in hand until they have now reached an altitude of 4,200 feet in the first instance and 3,000 in the second. This is the first authentic record we have of yellow fever reaching such an altitude and is another proof that, proper conditions supplied, the disease and the insect can be introduced and cause the same destruction of life as in more tropical regions. The destruction of this insect in our southern states has already been dwelt upon."

It should be understood that after Reed and his coworkers had demonstrated that yellow fever is disseminated only by the stegomyia, this discovery opened up and gave importance to the problem of the eradication of the disease. Quite naturally, it was evident that the first thing and the most essential thing to do was to destroy the mosquito. How to do this was then the great problem. Should all efforts be directed against the adult insect, or should an attempt be made to destroy the species in infected localities while in the process of coming into existence? So far as the adult mosquito is concerned much was done by screening the yellow fever patient and thus preventing infection of the mosquito. At the same time there was the possibility of reducing the disease by protecting nonimmunes against the bite of the adult, but since the stegomyia bites by day, little could be accomplished by this procedure. General Gorgas, health officer of Havana and later of the Canal Zone, did wisely in laying the stress of his work on the destruction of the mosquito by robbing the insect of its breeding-place. It is safe to say that if attention had been centered on protection against the adult mosquito to the exclusion of the destruction of its breeding-place, the splendid achievements that have been secured would not have resulted.

It must not be inferred from what has just been said that the fight against the adult mosquito was limited to exclusion by means of screens. Gorgas tells the following story concerning the employment of fumigation in Panama:

"Panama compared with Havana was a very small town. Havana in 1904 had a population of 250,000; Panama, about 20,000. Instead of waiting for the slow process

of fumigating the house where a yellow fever case occurred, with the contiguous houses, and thereby killing the infected mosquitoes concerned in that particular case, we ought to be able, we said, in a small town like Panama, to fumigate every house in the city within a comparatively short time, and thereby get rid of all the infected mosquitoes at one fell swoop. This would certainly have been the result if our premises had been correct, namely, that it was the fumigation that had caused the disappearance of yellow fever at Havana. With this object in view, we commenced at one end of the city and fumigated every building. It took us about a month to get over the whole town. Cases of yellow fever still continued to occur after we had finished. We therefore went through the procedure a second time. Still other cases occurred, and we went over the city a third time. We used up in these fumigations in the course of about a year some 120 tons of insect powder, and some 300 tons of sulphur. These quantities of material give some idea of the amount of fumigation. * * * An interesting incident occurred during this first year with regard to insect powder. Knowing there would be some yellow fever to be dealt with in Colon and Panama, we estimated and made requisition for eight tons of insect powder. The reviewing authorities were very much shocked and surprised at the size of our requisition, seized upon this one item of eight tons of insect powder to demonstrate the wildness of our estimates. It was some satisfaction to us for the commission to see that we had not only not been wild and extravagant in our estimates, but that we had been obliged to use actually 15 times as much as we had estimated."

Immunity.—There is probably no other disease to which such marked and lasting immunity is secured by one attack as yellow fever. The immunity is much more certain and more lasting than that which follows an attack of smallpox. One reason for this is the fact that the disease is always caused by the bite of an insect and the amount of infection introduced into the immune and the nonimmune is practically the same. With typhoid fever conditions are wholly different. Neither vaccination nor one attack of the disease gives so great an immunity that it may not be overcome by subsequent massive doses of infection. The man immune to yellow fever is still liable to puncture by the mosquito and if it be an infected mosquito a second dose is practically the same as that which induced the attack and gave immunity. In the second place, it is evident that the virus of yellow fever speedily and thoroughly sensitizes the body cells, which elaborate and make operative secretions having a destructive action on the invading virus. This is shown by the fact that the virus of the disease disappears from the yellow fever patient after three days. If after that time blood be taken from the patient in a syringe and injected into a nonimmune, the disease does not follow because the virus has been thus quickly and thoroughly destroyed in the man's body. This indicates thorough and rapid sensitization of the body cells and these cells continue in the possession of this newly acquired function throughout the life of the individual. It has been long observed in Havana and in other endemic centers of this disease that the local inhabitants are practically immune and that the disease is confined to nonimmune arrivals. The people of

Havana, at least the adult population, are immune to yellow fever simply because no one reaches adult life without having been inoculated with the virus through the agency of the mosquito; therefore, it happened in Havana that the number of cases of yellow fever increased with increase in new arrivals so far as these came from countries where the disease does not exist. In this way the great increase in the death rate from yellow fever in Havana following cessation of hostilities in Cuba in 1898 is accounted for. Thousands of nonimmunes reached the city from the United States and more from Spain. None of these possessed immunity and many of them speedily fell victims to the puncture of the stegomyia.

It will be remembered that in the experiments made by Reed and his colleagues no individual in whom yellow fever was induced by the artificial application of infected mosquitoes died, and with the exception of Carroll all had the disease lightly. It is true that Lazear developed a most virulent form of the disease and died, but his infection was due to the bite of a mosquito under natural conditions. With these facts in mind, there was an attempt made in Havana in 1901 to induce immunity to yellow fever by subjecting nonimmune arrivals, under artificial conditions, to the bites of infected mosquitoes. However, it was soon evident that this was not a safe procedure, because in a certain percentage of cases death followed experimental bites. It follows, therefore, that all the splendid work done in Havana, on the Canal Zone, at Rio, and at Guayaquil, has been accomplished without any further attempts to establish artificial immunity. The recent researches of Noguchi hold out great promise in the employment of a specific antitoxin, both for immunizing and curative purposes. It is to be hoped, however, that Noguchi's serum, however efficient it may prove to be, will meet with but little demand on account of the complete disappearance of the disease.

Before closing this chapter it might be well to mention one possibility which may render the extermination more difficult and further in the future than we anticipate. This is the possibility of there being a reservoir of the virus of this disease in some of the lower animals. Years ago Manson thought this possible and advised search for such an animal reservoir. Recently (1920) Balfour, on a visit to Trinidad, discusses the belief of the natives of that Island that epidemics of yellow fever are preceded and accompanied by a highly fatal disease among the red howler monkeys. It is to be hoped that this is only a negro superstition. On this point Balfour says:

"As I said before, there may be nothing in the idea, but I am told that in certain parts of Brazil a mortality in monkeys is known to accompany yellow fever outbreaks, and certain isolated outbreaks in Colombia could be explained on such an hypothesis. Man and the wild monkey rarely come into close contact, but they do so now and again,

as possibly in the high woods of Trinidad, and opportunities for infection might occur. When yellow fever raged at Gibraltar, in 1828, the monkeys, probably an African species, died in large numbers; but, of course, mortality amongst other animals has been noted in yellow fever outbreaks. Still, it is an interesting fact that the distribution of the genus *Alouatta*, of which *A. seniculus* is the red howler, corresponds in South and Central America fairly closely to the known distribution of endemic yellow fever. It may be a mere coincidence, but at least it would justify the experimental work I have suggested."

In 1921 Guiteras, most competent to speak upon this subject, called attention to discrepancies between Noguchi's discoveries and our present knowledge of the epidemiology of yellow fever. All attempts to control and eradicate this disease in the past have been founded upon the assumption that man and the *stegomyia* are the only carriers of the virus. Noguchi's work indicates that many animals, guinea pigs and dogs for instance, are susceptible to the disease. Guiteras asks, if this be true, how is it possible that there have never been manifestations of yellow fever among these animals in endemic centers and during great epidemic invasions. Guiteras furthermore points out that Noguchi's organism is easily inoculated through superficial lesions of the skin, whereas, since the discoveries of Reed, Carroll and their colleagues, all fears of inoculation at necropsy, in handling fomites, the excretions of the skin and the tissues of the dead, have been banished. These are questions which the future only can answer.

In discussing the eradication of malaria by the destruction of anopheles, we have included *antistegomyia* procedures.

Bibliography

- BOYCE, RUBERT: Mosquito or Man, London, 1910, John Murray.
GORGAS, W. C.: Sanitation in Panama, New York, 1915, D. Appleton & Company.
GUITERAS, J.: Jour. Am. Med. Assn., 1921, lxxvii, 397.
HOWARD, DYAR, AND KNAB: The Mosquitoes of North and Central America and the West Indies, Carnegie Institute of Washington, 1912.
KELLY, H. A.: Walter Reed and Yellow Fever, New York, 1907, McClure, Phillips & Company.
NOGUCHI, HIDEYO: Etiology of Yellow Fever, Jour. Exper. Med., xxix and xxx, Rockefeller Institute for Med. Research, 1919 and 1920.
YELLOW FEVER INSTITUTE BULLETINS: Government Printing Office, Washington, 1901-1909.

CHAPTER XXIII

DENGUE

Definition.—An acute, febrile disease, with sudden onset, short duration, and low mortality; prevalent in tropical and subtropical regions around the world. Dengue is distributed by a mosquito, *Culex quinquefasciatus* or, as frequently known, *Culex fatigans*, which is the most common tropical species of the genus *Culex*. It is possible also that dengue is spread by the *stegomyia*.

History.—In the early Spanish literature concerning disease in this hemisphere, mention is occasionally made of the prevalence of a mild form of yellow fever. We have no authority to speak with certainty in this matter, but it is highly probable that the disease then observed and thus described was dengue. On both sides of the earth, notably by Rush in Philadelphia and by Boylon in Java, what we now know as dengue was described in some detail late in the eighteenth century. Both authors called it a bilious fever. However, the first unequivocal description of the disease was written by Dickson in 1828. During the following 50 years there appeared at long intervals papers on this disease, some claiming that it possessed a distinct identity, while others questioned its existence as an entity. It is interesting to remark that during all this time in the few papers that did appear, those who observed the disease, for the most part at least, were quite confident that it is not contagious in the ordinary sense but that it is transmissible.

To Graham, of Beirut, Syria, is due the credit of first approaching the study of the disease in a scientific way. Beirut, as is well known, lies on a narrow plain backed by high mountains. The plain, including the city, is infested at certain seasons of the year with *C. quinquefasciatus*. After some preliminary investigations Graham succeeded in obtaining four volunteers. Each of these slept under a mosquito netting into which insects which had recently bitten patients with dengue were introduced. Three of the individuals manifested undoubted symptoms of the disease within from four to six days after exposure to the bites of these mosquitoes. Notwithstanding that the fourth man passed 15 consecutive nights exposed to the infected mosquitoes he did not develop the disease. Graham found that this man remembered having had a relatively severe attack of the disease some three years previously and consequently must have been immune. Graham was not altogether satisfied with the results of this experiment, and we shall permit him to continue his own story as follows:

“In a city where so infectious a disease was raging I still felt that these three men might have received the contagion in some other way. In order to avoid this objection mosquitoes were taken from inside the netting of a dengue patient and carried up to a village on the mountain slope where as yet no case had occurred. After visiting my patient for the infected mosquitoes I changed my clothing and took a bath before mounting my horse to ascend the mountain. In this village, about 3,000 feet above the sea, there are *almost* no mosquitoes. It is dry and very healthy. I easily found two young men in different parts of the village who consented for a consideration to take their chances of having the dengue. One of them, after sleeping four nights under the netting with the mosquitoes, was taken with a severe typical attack of dengue. The other had his initial chill after having passed five nights in the company of the mosquitoes. These men continued to sleep under the mosquito netting I had prepared for them until some time after they were well, all the mosquitoes in the net having been killed to avoid infection of other people. No other case of dengue occurred in this village during the summer that I could learn of, although I made the most careful inquiry.”

Graham examined the blood in more than 100 cases of dengue and believed that he discovered a parasite resembling in some respects plasmodium malariae. He reports this parasite as first appearing as a small rod or dot within the red-blood corpuscle, constantly changing its position, the motility in some instances being marked; later, the parasite increases in size, shows typical amoeboid movements, more nearly fills the corpuscle, and then either degenerates or ruptures the corpuscle and escapes into the plasma. He was unable to find any evidence of the formation of spores. By dissecting and examining the blood contained in their stomachs, Graham reported the finding of piroplasma-like bodies in the mosquito up to the fifth day after the biting. Furthermore, he inoculated a man with an emulsion of the salivary glands of an infected mosquito and produced a disease so alarming that he desisted from further experimentation along this line.

Graham's reports attracted wide attention and stimulated investigation into the etiology of this disease. No one has confirmed the finding of the parasite reported by Graham. The blood has been carefully studied by Stitt, Ashburn, Craig, and others. No abnormality in the blood corpuscles, and certainly no parasite, either in the corpuscle or in the plasma, has been detected by any one else. On account of the failure to confirm this phase of Graham's work there has been a tendency to discredit everything that he did. However, experiments repeatedly made in various parts of the world have confirmed the work of Graham so far as it relates to the transmission of the disease by *C. quinquefasciatus*. It appears from recent researches by Cleland and others in Australia and by Archibald in the Sudan that the virus of this disease is distributed, in these localities at least, by the *Stegomyia fasciata* instead of by the *culex*. No one, so far as we know, has implicated the anopheles.

Probably the most extensive work along this line has been reported by Ashburn and Craig, working in the Philippines. These investigators have shown that either whole or filtered blood from patients with dengue when injected into nonimmunes induces the disease. Furthermore they have confirmed Graham's findings by being able to transmit the disease through the bite of *C. quinquefasciatus*. They endeavored to develop the disease by exposure of healthy men to fomites, the men experimented with living in mosquito-proof tents with patients suffering from dengue throughout the entire course of the disease. They slept in their beds, wore their underclothing and pajamas, and ate and drank from the same tableware. Eight men were carried through this experiment of exposure to fomites and all remained well. The conclusion, therefore, is reached that dengue is not a contagious disease and that patients suffering from it may be placed in the general wards of hospitals without fear of infection, provided precautions are taken to protect them from mosquitoes.

The conclusions reached by Ashburn and Craig are stated as follows:

"After a thorough examination of the blood of numerous patients with dengue we concluded that it did not contain any visible organism either bacterial or protozoal in nature, which could be considered as the cause of the disease. Our attempts at securing blood cultures also resulted negatively and in order to determine whether the cause of this fever was present in the blood we were forced to attempt the production of the disease by the inoculation of the blood from dengue patients into healthy individuals. As the disease is one which in the young and robust is not dangerous to life, we felt justified in making such experiments, and had no difficulty in procuring volunteers for this purpose. We first undertook to study the effect of the intravenous inoculation of unfiltered dengue blood. Eleven men were inoculated, and in seven a typical attack of the disease developed, while one case was doubtful. * * * These experiments proved beyond question that the cause of dengue is present in the blood of infected individuals, as the intravenous inoculation of such blood in healthy men is capable of producing a typical attack of the disease. As our examination had proved that it was impossible to demonstrate a parasite in the blood we concluded that it must belong to the class of so-called ultramicroscopic organisms and in order to determine this point we inoculated two healthy individuals with filtered blood from dengue patients, with the result that severe attacks were produced in both men. In our filtration experiments we employed a Lilliput filter which was tested and controlled each time it was used, and the filtration was done under 730 millimeters pressure. After filtration a control test was made of the filter by using a bouillon suspension of *Micrococcus melitensis*, the filtrate then being incubated for two weeks, and examined every day. The filter we used retained this organism, so that it may be stated that the virus of dengue, passed through the pores of a filter which prevented the passage of an organism measuring 0.4 miera in diameter. The blood from the dengue patients was defibrinated and diluted with an equal amount of normal salt solution, and the filtrate was introduced intravenously. In both of the men inoculated with the filtrate the attack was of a severe character, and we regarded these two cases of dengue, produced by the intravenous injection of filtered dengue blood, as the most typical cases of the severe type of the disease which we observed.

These experiments proved that the organism causing the disease is probably ultra-microscopic in size, and this conclusion explains the uniformly negative results obtained in the search for the parasite. We concluded that an organism was present in the filtrate, rather than a toxin, because of the length of the period intervening between inoculation and the appearance of clinical symptoms, and also because one of the men was inoculated with the filtered blood of an experimental case of dengue produced by the intravenous injection of unfiltered blood from a naturally infected dengue patient. * * * Owing to the subsidence of the epidemic we were unable to continue our mosquito experiments, which are therefore incomplete, but, taken in connection with those of Graham, prove that this disease may be transmitted by the mosquito. We felt justified in concluding that this method of transmission is the only natural one which has been proved by experiment, and which agrees with the epidemiology of the disease. We were further able to show experimentally that natural immunity exists against this disease, and that it is not contagious. We exposed eight healthy men to fomites, the men experimented with living in mosquito-proof tents with patients suffering from dengue, throughout the entire course of the disease. They slept in their beds, wore their underclothing and pajamas, and ate and drank from the same table furniture, but none of them developed the disease.

"Our conclusions regarding the etiology of dengue were partly as follows: (1) No organism, either bacterium or protozoan, can be demonstrated in either fresh or stained specimens of dengue blood with the microscope. (2) The intravenous inoculation of unfiltered dengue blood into healthy men is followed by a typical attack of the disease. (3) The intravenous inoculation of filtered dengue blood into healthy men is followed by a typical attack of the disease. (4) The cause of the disease is, therefore, probably ultramicroscopic. (5) Dengue can be transmitted by the mosquito, *Culex fatigans*, Wied. (6) No organism of etiologic significance occurred in bouillon or citrated blood cultures. (7) The period of incubation in experimental dengue averages three days and fourteen hours. (8) Certain individuals are absolutely immune to dengue, as proved by our experiments. (9) Dengue is not a contagious disease, but is infectious in the same manner as is yellow fever and malaria."

Immunity.—From the earliest recognition of this disease it has been noted that one attack gives permanent immunity. There may be exceptions to this, as there are in most diseases; in fact, there is, even at present, no positive scientific test for the recognition of this disease. It is, therefore, quite impossible to be sure about the permanency of the immunity secured by one attack. All through its history in regions where yellow fever coexists, it has been observed that an attack of either of these diseases gives no immunity to the other; indeed, this has been a strong point in the differentiation between the two diseases. As we have already seen, early in the medical history of the Western Hemisphere dengue was by some regarded as a mild form of yellow fever, but when it was shown that an attack of the former gives no immunity to the latter this theory was abandoned.

Prophylaxis.—It is unnecessary to go into detail concerning methods for controlling and eradicating dengue. They are the antimosquito

procedures, which have been so fully discussed in the chapters on yellow fever, malaria, and other mosquito-borne diseases.

Bibliography

- ASHBURN AND CRAIG: Phil. Jour. Sc., 1907, ii, 93.
DICKSON, S. HENRY: Am. Jour. Med. Sc., 1828, iii, 3.
GRAHAM, H.: Jour. Trop. Med., 1903, vi, 209.
STITT, E. R.: Phil. Jour. Sc., 1906, i, 513.

CHAPTER XXIV

THE TRYPANOSOMIASES

Definition.—Under this term we include all those departures from health, some benign and scarcely recognizable, others distressing and highly fatal, which result from infection with some species of the genus *Trypanosoma*. There are numerous species of this widely distributed parasite and likewise many invertebrate and vertebrate hosts, but up to the present only three species are known to seriously infect man. These are *T. gambiense*, *T. rhodesiense*, and *T. cruzi*. The first two are distributed by flies belonging to the genus *Glossina* (*G. palpalis* and *G. morsitans*) and are confined to Africa. The third is distributed by a bug, *Conorhinus megistus*, and up to the present has been found only in South America. There are many other species of trypanosomes which cause more or less serious diseases in the lower animals, and it is possible that further study will show that some of these may infect man.

African Trypanosomiasis or Sleeping Sickness.—It appears that the first mention of this disease in the English language is found in a book, entitled, “The Navy Surgeon” by Atkins, published in 1734 and giving an account of “the sleeping distemper” which he observed among the negroes of the Guinea Coast in 1721. It is more than probable that the west coast of Africa, certainly from Senegal in the North to the Congo Free State in the South and extending inland to the Upper Niger and to the Stanley Falls of the Congo, has been afflicted with this disease for many generations. Visitors are told by the natives that tradition does not antedate the existence of this disease. In 1858 Livingstone found that many African tribes reported the “tsetse fly” disease as long prevalent among them. A more certain proof of its long continued existence among the people of this region is to be found in the fact that each tribe has a specific name for the disease. In 1803 Winterbottom saw this disease on the west coast of Africa near Sierra Leone and observed that slave dealers refused to buy those who had enlarged cervical glands. It seems, however, that the inspections made by the slave drivers were not altogether successful in excluding the diseased individuals, because during the first half of the nineteenth century cases were occasionally reported from the West Indies and it was observed that they were found only among those who had been imported from Africa and never in the second generation. An especially noteworthy contribution on this subject is that of Guérin (Thesis, Paris, 1869) who described a large number of cases of sleeping sickness

among the negroes of Martinique. African sleeping sickness cannot spread in the Western Hemisphere, because the essential distributor of the disease, the tsetse fly, does not exist on this side. In 1876 Corre studied and described the disease as it existed at that time in Senegambia. In 1891 a case was brought from Africa to London where it was studied by Mackenzie. In 1900 two more cases were brought to London under the care of Manson who, with Mott, investigated the etiology, symptomatology, and morbid anatomy of the disease. The disease was apparently carried into Uganda and Busoga from the upper reaches of the Congo by the returning followers of Emin Pasha (1891-1896). The tsetse fly had long been prevalent and well known in the region about Lake Victoria Nyanza, but the disease in this region was rare or unknown. The Cooks had established a hospital in Uganda about five years previously, but the disease when it came in 1901 was new to them. From 1900 to 1909 sleeping sickness killed many thousand natives living on the islands and shores of the lakes. It is estimated that in 1902 out of a total population of 44,311 on the Buvuma Islands, 19,049 died of sleeping sickness. This makes a death rate of 428 per 1,000, one of the highest death rates, even for an epidemic disease, recorded in the annals of medicine. So serious was the problem that the Government of the Protectorate forcibly moved the natives from the islands and shores of the lake into the interior, it being found that the flies seldom left the water for a distance of more than two miles. The assumptions upon which these drastic measures were based were given as follows: (1) The disease is not transmitted in districts where the tsetse fly is not found. (2) The presence of even a single diseased person in a locality infested by the flies may lead to the infection of the whole community. (3) The disease is incurable. (4) The tsetse fly being the indispensable link in the chain of infection, cutting it out was the only alternative. (5) On certain islands largely infested by the flies the entire population had already disappeared. It seems that these measures were at least partially successful. They were followed by a marked decrease in the deaths, because there were no people left to die, and it disappeared among those who were removed. The death rate from this disease in Uganda has decreased rapidly and since 1910 a case is rarely seen.

In the endemic area on the west coast of Africa the disease is recognized as existing in three stages. In the first, there is but little, if any, disturbance of health. Most infected individuals will show no symptoms and will declare that they feel perfectly well. In others, there is an occasional run of a light intermittent fever, accompanied by muscular weakness and increased rapidity of pulse and respiration, especially after slight exertion. There is no mental dullness or hesitancy in expression. The only evidence

of abnormality that can be found in these cases is an enlargement of the superficial cervical glands. In blood drawn directly from these glands, more rarely in that of the peripheral circulation, trypanosomes are found. In the second stage, the irregular fever manifests itself more frequently and occasionally becomes a remittent or low continued type. Individuals are still well nourished unless there be some coexisting disease. The heart beats and the respiration are more easily quickened and exhaustion is more evident after slight physical exertion. There is as yet no marked mental dullness, although patients may show carelessness and untidiness. Manson has noticed in Europeans in this stage, an erythematous rash, sometimes with transient edema; but in natives the skin is only dry and rough. The cervical glands are still enlarged and may show some increase in size over that evident in the first stage, but even this is not constant. The parasites are more likely to be present in large numbers, both in the blood obtained from the enlarged glands and in that drawn from the periphery. It is not until the third stage is reached that the clinical picture which gives the name to the disease appears. There is marked dullness of intellect; the patient rests in an apathetic state, has a vacant look, and answers questions with marked hesitation. Actual sleepiness is not as much in evidence as the lack of interest in what is going on about him. The patient may be easily aroused, takes food with relish, and apparently digests it with ease. With the progress of the disease mental dullness intensifies and finally a comatose condition precedes death. In the third stage there may be a mild form of mania, with retraction of the head and possibly opisthotonos. Tremor of the hands and tongue is frequently in evidence. In the first and second stages, the parasites are present, though often found with difficulty, in the circulating blood; while in the third stage they have reached the arachnoid space and have developed a chronic cerebrospinal meningitis, accompanied by a mononuclear cellular infiltration of the membranes and surface of the brain. It is from this involvement that the symptoms which give rise to the popular name of "sleeping sickness" develop. It is believed that when this stage is reached the disease is always fatal. In the third stage, the parasites appear in the cerebrospinal fluid and may be demonstrated after lumbar puncture. The parasites are sometimes so abundant in the cerebrospinal fluid that it is not necessary to take any precaution in recognizing them. However, it is best to centrifuge the fluid in order to be sure that they do not escape detection.

In 1911 Todd and Wolbach were sent by the Liverpool School of Tropical Medicine to the Colony of the Gambia to determine the incidence of the disease in that territory, to discover the best method of recognition of the disease and to point out preventive measures. The Protectorate of the Gambia consists of a narrow strip of land on each

side of the river of that name extending from its mouth to a distance of about 200 miles into the interior. It covers an area of about 5,000 square miles and the estimated native population in 1911 was 200,000. The dry season lasts from November to June, during which time there is but little water in the country; swamps dry up and the river becomes little more than an arm of the sea, the tides being felt 240 miles inland. During the rainy season the river and its tributaries often overflow their banks, the lowlands become swamps and marshes, and a great part of the surface is covered by tropical jungle. The river and its creeks constitute the high roads of travel and their margins are clothed with mangroves, bamboo and scrubby growths. Of the people, Todd and Wolbach write:

"All the tribes in the Gambia are very prosperous. Their cattle have increased enormously in number and their land is fertile. They raise good crops of millet and rice for their own use, and large amounts of ground-nuts which are sold to traders for export to Europe. With the money obtained from the sale of ground-nuts the natives are able to buy all the European articles, such as cloth and powder, which they require. Because of the favorable conditions for obtaining money by the sale of ground-nuts, large numbers of young men yearly come to the British territory in order to make farms and raise crops of ground-nuts. They come from French territory, from all directions; some of them come from places distant eight, and even more, weeks' travel."

These investigators found that the detection of the parasites is most certainly secured by puncture of the enlarged glands. They estimate that about .8 per cent of the people are infected with *T. gambiense*. Sleeping sickness has never, so far as is known, been epidemic in its original home on the west coast of Africa. The most likely conclusion to draw from this is that the people of this region, long subjected to this infection, have acquired a certain degree of immunity. On this point, Todd and Wolbach remark:

"The fact that trypanosomiasis has been present in the Gambia and elsewhere on the west coast of Africa for many years, in places where *Glossina palpalis* exists, without assuming the epidemic form which it has taken in the Congo Free State and in Uganda, of itself, suggests that the west coast natives may have acquired some immunity to it. In the Gambia the custom of the natives, almost none of whom were riverine, has doubtless much to do with preventing the spread of trypanosomiasis; but there seems to be something more than that. There are many records, some based altogether on the observations of Europeans, others based on observations of natives and of Europeans, of persons who have lived for four or more years after they probably became infected by trypanosomes; these records prove that persons may have a tolerance for trypanosomes and live comparatively healthily though infected by them."

Todd and Wolbach recommended that certain towns should be moved to localities more distant from water and forests. Furthermore, they suggested that all growth be cleared from the neighborhood of fords, wharves, or places where native women assemble to do their laundry

work. All such places should be at least 150 yards from the nearest bush. It is suggested that the growth of marsh rice be prohibited and that mountain rice be substituted, or, since rice is not an important product, its growth be altogether discontinued. Those who are infected should be isolated and protected from the tsetse fly. Infected persons should be prevented from going into regions where the disease does not exist but which are infested with the flies. In carrying out a quarantine with this object in view reliance should be placed upon the presence of enlarged cervical glands. Individuals showing these defects should not be allowed to pass unless examination of fluid obtained from the glands shows no trypanosomes.

In 1919 Duke made a report upon sleeping sickness in Uganda and neighboring territory. He points out that the deaths among those who had been removed from the islands and margins of the lakes ranged from four to six per cent, while it was assumed at the time of their removal that ninety per cent of them were infected. It follows, therefore, that we must conclude that by far the larger percentage of those infected have recovered. The conditions on the islands and the shores of the lakes were most favorable for the transmission of the infection directly by the fly from individual to individual and the chance of escaping such infection was small. The people of this region at the time of the appearance of the epidemic and until their removal spent a great part of their time in canoes passing to and fro from shore to island, and in fishing. Duke says:

"When a canoe is pushed off from a fly infested shore (and the canoe landings on Victoria Nyanza were notoriously densely infested), or if it passes close in to such a shore, a small—sometimes a large—swarm of flies will come off and follow it to open water. The flies will not come off to a passing canoe more than 100 yards or so from shore, neither will they freely leave a canoe that they have followed to a greater distance from shore, but will accompany it for hours. Under these conditions more may feed on the crew than if the same crew remained on the beach, and it is the commonest sight under these conditions to see one paddler after another dislodge a biting fly, which, in the course of a few minutes may have bitten several men. Conditions for 'mechanical transmission' are absolutely ideal—as favorable in proportion to the number of flies involved as could be reproduced in the laboratory. It is proved by laboratory experiments that this species of fly can transmit this species of trypanosome with a certain facility under such conditions; and it is not only possible or plausible but virtually certain, that mechanical transmission in canoes must have occurred with frequency and regularity during the early stages of the epidemic. The riparian populations of Uganda possessed many hundreds, probably several thousand, canoes, which were in constant use for fishing and commerce. They also fished, in parties, from fly infested shore; gathered in numbers for repairing canoes, fishing gear, etc., under similar conditions; and finally there were market places where islanders met mainlanders for exchange of produce, at points on the shore that were well known to be densely and dangerously infested by flies."

In 1904 Greig reported that the sleeping sickness beginning on the shores of Victoria Nyanza had extended with diminishing severity along both banks of the Victoria Nile as far north as Wadelai, where the presence of *G. palpalis* reached its limit. However, *G. morsitans* is found in the Upper Sudan, and it is possible, though this has not been demonstrated, that this fly may transmit *T. gambiense* from man to man. *G. palpalis* was reported before the World War in Arabia. If this be true, it is within the range of probability that African sleeping sickness may appear in that country. So far as we know, *G. palpalis* is not found in any part of the world other than the region which we have indicated in Africa, and possibly in Arabia. It is highly probable that it will be found that other trypanosomes do infect man and are transmitted by other invertebrates.

In 1901 Forde and Dutton found trypanosomes in the blood of a patient suffering from an irregular fever on the Gambia River. One year later Castellani, working in Uganda, found a trypanosome in the cerebrospinal fluid of a man suffering from sleeping sickness. It seems, however, that this observer did not at the time consider any causal relationship of this parasite to the disease but regarded it as an accidental concomitant. Bruce, who had previously studied the tsetse fly disease among cattle in southern Africa, at once recognized the possible importance of a trypanosome in the blood and in the cerebrospinal fluid in cases of sleeping sickness. Investigation showed that the subcutaneous injection into monkeys of the blood of patients containing trypanosomes (although the individual at the time showed no symptoms) and of the cerebrospinal fluid in undoubted cases of sleeping sickness, caused the disease in these animals. Further experimentation demonstrated that the same effects followed whether blood or cerebrospinal fluid was employed, provided they contained the trypanosome. The next problem was to ascertain the carrier of the parasite. Bruce, with the experience of his previous work on fly disease among cattle, quickly suspected and then incriminated *Glossina palpalis*. These flies were permitted to feed upon patients suffering from sleeping sickness and then caused to bite monkeys. By this procedure the disease was transmitted to the animals. Moreover, the developmental stages of *T. gambiense* in the alimentary canal of the tsetse fly were studied. In 1910 Stephens and Fantham found in Rhodesia a new species of trypanosome, to which the name *T. rhodesiense* was given. Two years later it was shown by Kinghorn and Yorke that this trypanosome is transmitted by *G. morsitans*; therefore, so far as African sleeping sickness is concerned there are two trypanosomes, *T. gambiense* and *T. rhodesiense*, which are transmitted respectively by *G. palpalis* and *G. morsitans*.

In the history of his African explorations, Livingstone states that he observed horses suffering from a disease called by the natives "nagana." He found the administration of arsenic of great benefit to these horses. In 1895 Bruce demonstrated that "nagana" is due to infection with a trypanosome. This was also shown to be the case in "surra," as this disease is known in India. Putting these facts together, arsenic in various forms has been largely employed in the treatment of sleeping sickness. In 1905 Thomas demonstrated the value of atoxyl, an arsenical preparation, in the treatment of experimental trypanosomiasis in animals. This and other arsenical preparations, including arspheamine, have been employed, apparently with marked benefit, in the treatment of the disease. More recently, tartar emetic and other antimonial preparations have apparently given even better results.

Trypanosomes.—There is an almost endless number of species of parasites belonging to this genus. They are not only numerous, but they exhibit marked variations in form, size, and in effect upon their hosts. The first parasite of this genus was found in the blood of frogs and was described by Gruby as long ago as 1843. His description reads as follows:

"Its elongated body is flattened, transparent, curved like a centre-bit; the cephalic end is terminated in a thin, elongated filament; the caudal end is terminated also in a pointed filament. The length of the animal is 40 to 80 microns. Its breadth is 5 to 10 microns. The filamentous pointed cephalic end has the greatest mobility. The length of the cephalic filament is 10 to 12 microns; its body is elongated, flat, and toothed like the blade of a saw all along the length of one of its margins. It is, as I have above mentioned, supple and twisted two or three times around its axis, like an augur or corkscrew, which is the reason why I propose to name this *hematozoön*, *trypanosoma*."

In a general way trypanosomes, as found in the blood of vertebrates, consist of spindle-shaped masses of cytoplasm composed of an inner granular endoplasm and an outer ectoplasm. In the endoplasm there are two nuclear bodies. The larger, known as the trophonucleus, is in the majority of species situated near the middle of the endoplasm, while the smaller, the kinetonucleus, is located near the anterior end of the parasite. However, in different species the relative location of these two bodies differs greatly. At one end of the parasite is a long flagellum, a continuation of which forms the border of an undulating membrane and ends at the kinetonucleus. The undulating membrane is, therefore, a layer of ectoplasm raised from the surface of the parasite and terminating anteriorly at the base of the free flagellum. In certain species there are chromatoid granules in the endoplasm. In most species these are most abundant posteriorly to the trophonucleus. All trypanosomes require for their full development two hosts, one of which is a vertebrate and the other a blood-sucking invertebrate. When a clean

vertebrate is infected by an infested invertebrate no parasites are to be found in the peripheral blood until an interval of some days. This is known as the incubation period. What happens during this time is not certainly known. There is probably some form of multiplication, but sooner or later the parasites appear in the peripheral blood where they show marked variation, according to species, in form. Even in the same species, as for instance *T. gambiense*, there may be short spindles not more than 14 microns in length, medium forms 20 microns and long forms 33 microns. These differences in size have been thought by some to be due to different sexes, male, female, and neutral. The usual form of multiplication of the trypanosome in the blood is by longitudinal fission. The number of parasites in the blood of an inoculated animal varies widely from time to time, and it is supposed that they may disappear from the blood to undergo a period of encystment in some tissue. There is still some difference of opinion as to sexual reproduction in the blood of the vertebrate. It is believed by some investigators that the very slender, highly motile trypanosome with an elongated nucleus is the male; that the broad, slowly moving, parasite, with a round nucleus and possessing a short flagellum, is the female; that the forms most commonly met with, showing granular cytoplasm and no well-defined nucleus, are neutrals. It is true that sexual conjugation is reported to have been seen under the microscope by certain observers. However, it is by no means certain that the movements observed indicate sexual union, and it is thought by some good observers that the phenomena observed are connected with longitudinal fission rather than with copulation.

Most trypanosomes are apparently quite harmless to their vertebrate hosts. A number of animal diseases in which this is not the case will be referred to later. Those which are known to cause disease in man are *T. gambiense* and *T. rhodesiense*, the causes of African sleeping sickness; *T. cruzi*, the cause of South American trypanosomiasis.

T. gambiense as found in the blood or cerebrospinal fluid of man varies in length from 14 to 33 microns and in breadth from 2 to 2.5 microns. However, it displays remarkable evidence of polymorphism. The posterior end varies in shape and in size, sometimes quite pointed and in other instances quite rounded. The trophonucleus is oval in shape, located about the middle of the body and in front of the chromatic granules in the cytoplasm. The kinetonucleus is oval and behind it there is often a visible vacuole. The life history of this parasite in the human body has not been completely studied. As has been stated, the trypanosome is sometimes found in the peripheral blood, but in other instances most careful search of this fluid fails to demonstrate it. It is more frequently and easily found in the juice of the enlarged

cervical glands, and in the third stage of the disease it is present in the cerebrospinal fluid. In experimental inoculation in the rat this parasite gradually increases in the peripheral blood, then declines in numbers and finally disappears altogether for a period. During this latent period the trypanosome may be found especially in the spleen and bone marrow in which the protoplasm becomes detached from the periphery of the nucleus. The rest of the cell body disintegrates and the flagellum with the kinetonucleus may be altogether detached. These forms have been called by Moore and Breinl "latent bodies." They show a flattened nucleus containing a centrosome attached to a vesicle, the whole being surrounded by a ring of cytoplasm. The centrosome inside the nucleus divides, escapes from the nucleus, and becomes the kinetonucleus, which develops into the form found in the blood.

The evolution of *T. gambiense* in the tsetse fly is apparently both complicated and precarious. One of the latest writers on this subject, Duke, makes the following statement:

"During the earlier stages of this cycle the insect is incapable of conveying the parasite to susceptible hosts upon which it feeds. A condition is finally produced when the parasite is established in the salivary glands of the fly which is henceforward infective, as far as known, until its death. There is a large amount of evidence to show that in only a small percentage of *Glossina palpalis* is the trypanosome capable of undergoing cyclical development. The highest percentage of positive flies that we have obtained in any laboratory feeding experiment was 20.6. Miss Robertson gives 3.4 as the average percentage of positive flies given with the Uganda strains of what is generally presumed to be *T. gambiense* in laboratory bred flies. Frequency of the infecting feedings appears to make no difference in the resulting percentage of positive flies. In the above percentage calculations any fly showing multiplication of trypanosomes in its gut is classed as positive. A large proportion of these, however, die before invasion of the salivary glands with infecting forms had occurred. In the course of the investigations of the Commissions of the Royal Society a large number of experiments have been carried out to determine the percentage of wild flies carrying a polymorphic trypanosome, which appears from laboratory evidence identical with the organism which caused the epidemic. Experiments conducted with wild flies caught near Entebbe in 1903, where the natives were considered to be infected with trypanosomes in the proportion of one in every three or four, revealed a percentage of 0.3 positive flies; 0.1 per cent of positive flies resulted from experiments performed in May, 1911, with flies from Damba Island, in the Sesse group."

So far as the evolution of *T. gambiense* in the fly has been made out it runs as follows: The trypanosomes multiply in the midgut, developing into long highly motile bodies which between the twelfth and twentieth days find their way into the salivary glands. Here they become attached to the walls and suffer fission, leading to the formation of minute trypanosomes similar to those which are seen in the blood. According to Robertson, the development within the salivary glands of the fly requires from two to five days, and this happens in only about

eight per cent of flies experimentally infected. Concerning the development within the fly, Duke makes the following statement:

"The trypanosomes on entering the gut of a fly suited to their cyclical development multiply enormously by division. This process is continued for at least 17 days and finally the forms infective to a new host are found in the salivary glands of the fly. The gulf separating these salivary gland forms from the original infecting trypanosomes is, biologically speaking, enormous. It is reasonable to suppose that none but specific and deep-rooted characters could survive such a drastic ordeal. The question of the transmission of acquired characters through the insect intermediary has not been properly worked out for the hematozoa. Gonder's experiments with *T. lewisi* are, however, most instructive in this connection. He found that a strain of lewisi whose resistance to arsenic had survived 20 passages, lost this property when transmitted cyclically by lice. The same strain when transmitted by the lice from rat to rat by the direct method retained its arsenic resistance."

The tsetse fly transmits human trypanosomes either directly or cyclically. It has been abundantly shown that immediately after feeding upon an infected man or animal *G. palpalis* may mechanically transfer the trypanosome to a new host. Duke says that there is, so far as known, no other biting fly whose mouth-parts are adapted to the transmission of trypanosomes which can compare with glossinae as a disseminator of the disease by the direct method. When interrupted during its meal on one man *G. palpalis* with unsatisfied appetite eagerly and even daringly seeks another individual from whom it may draw further food. We have already referred to something like this in speaking of the infection of the natives in the canoes on Victoria Nyanza. There is some reason for suspecting that the parasite, when transmitted mechanically and directly, is more virulent than when transmitted cyclically; indeed, in his recent report, Duke is inclined to deny that there is any positive evidence that an infected fly has ever transmitted sleeping sickness to man cyclically. In experiments on animals, however, the cyclic transmission is fully established. This is one of the many problems still connected with this disease and its transmission which must await solution.

T. rhodesiense differs but little morphologically from *T. gambiense*. The principal difference is in the relative location within the endoplasm of the trophonucleus and the kinetonucleus. These are closer together in *T. rhodesiense* than in *T. gambiense*, and in the former it occasionally happens that the trophonucleus is found between the kinetonucleus and the aflagellar end of the parasite; in other words, the relative position of these two bodies is changed. The development of this parasite in both the vertebrate and invertebrate hosts does not differ in any material way from that of *T. gambiense*. This parasite occurs not only in man, but in certain domestic animals, as cattle, and in big game, such as antelope, hartebeest, etc.

T. cruzi.—This trypanosome, discovered by Chagas in 1909, has for its invertebrate host a bug, *Conorhinus megistus*, formerly known as *Lamus megistus*, and has been shown to be the cause of South American trypanosomiasis. In the peripheral blood it appears in two forms, free and in the red blood corpuscles. The free parasites are seen in two forms, one with a large oval kinetonucleus and with a band-like trophonucleus. The second is smaller, has no kinetonucleus, and is without an appendix. It is supposed by some that these forms represent male and female. This trypanosome is not known to multiply by longitudinal fission. According to Chagas, the cyclical development of this parasite occurs in the lungs. The asexual reproduction is believed to take place in the tissues of various organs, such as the striped muscles, the lungs, and the nervous system. In these localities the parasite appears as an oval or rounded body with kinetonucleus and trophonucleus, but without undulating membrane or flagellum. In the invertebrate host the parasite is able to develop both sexually and asexually. Chagas reports that he has been able to infect guinea pigs, rabbits, cats, and dogs by the bites of the infected insects. The insect is voracious; attacks people, especially children, at night, and since the bites are generally upon the face, the insect is known locally as "the barber." The disease begins with an acute fever, showing a morning fall and an evening rise. This is accompanied by edema of the face, manifesting marked crepitation. There is an enlargement of the thyroid and of the cervical glands. There may be transient edemas in different parts of the body. Both spleen and liver are enlarged and the former often becomes painful. The fever, which is at first continuous, becomes remittent with periodic intervals. During the fever the trypanosomes can be found in the peripheral blood, from which they disappear during the afebrile period. This is known as the acute disease, from which the child dies or passes into a chronic stage. Chronic South American trypanosomiasis manifests itself in several forms. One of these, known as the myxedematous form, is characterized by atrophy of the thyroid gland with the usual symptoms of myxedema. The skin becomes rough, the hair falls out, there is an arrest of mental development in children and evidences of mental deterioration in adults. The lymphatic glands in various parts of the body are enlarged, and this form is often accompanied by inflammatory disease of the eye.

In the second form, known as pseudomyxedema, there is hypertrophy of the lateral lobes of the thyroid gland; more infrequently, enlargement of the central lobe. In a child the skin takes on a peculiar bronze coloration; sometimes a violet bronze. These peculiarities in the color of the skin are believed to be due to invasion of the suprarenal capsule by the parasite. The cervical, axillary, and groin glands may be

enlarged. In the third or cardiac form, the most striking abnormality is associated with the heart's action, in which there is extra systole.

In the fourth or the nervous form, there are symptoms which indicate disturbances and abnormalities in the brain and spinal cord. There is a fifth or subacute form, in which there is a continuance of the fever with marked exacerbations. This form is accompanied by a high mortality and is marked by the infrequency with which the parasite is found in the peripheral blood. According to Chagas, infantilism is a sequel to the disease. This disease is often confounded with hookworm. Sometimes the two diseases appear in the same individual.

So far, we have considered the three trypanosomes which are known to invade the human body. We shall follow this with short mention of some of the trypanosomes known to cause disease in the lower animals.

T. evansi was discovered by Evans in India in 1880, and since that time it has been demonstrated to be the cause of a disease known as "surra," which infects camels, mules, horses, and cattle in India, Java, and the Philippines. This parasite generally measures about 25 microns in length, 1.5 microns in breadth, and has a pointed head and a long flagellum. It is actively motile and multiplies by fission. According to Holmes, there are male and female forms which conjugate by union of the posterior extremities, after which the female splits into amoeboid bodies that develop into trypanosomes in the liver, spleen, and bone marrow. *T. evansi* apparently has for its invertebrate hosts both fleas and flies. It causes a fever which is either remittent or intermittent in character and is accompanied by marked muscular weakness and followed by paralysis and death.

T. brucei, discovered by the Bruces in 1895, is the cause of the disease known in Zululand as "nagana," and which is common among horses and mules in that country. This trypanosome is transmitted by *G. morsitans*, which is widely distributed over a large part of central and southern Africa, especially in Zululand, the Transvaal, Pretoria, the Valley of the Zambesi, and in German and British East Africa. It is said that this parasite, which in horses and mules varies in length from 28 to 33 microns, differs constantly in length according to the host in which it is found. It multiplies by longitudinal division. In addition to being disseminated by the bite of *G. morsitans*, it is spread by eating the flesh of animals dead from nagana. Some highly competent authorities insist that *T. evansi* and *T. brucei* are the same, or, at most, their differences do not justify different species.

T. equinum is the cause of a disease seen in dogs and horses in South America and known under the name "mal de caderas," which means disease of the hind quarters. This is a highly fatal disease among horses and mules in South America. At first, there is fever. While the appetite

remains good the disease makes rapid progress and soon the animal is dragging its posterior extremities. Horses may live from six to eight weeks after the paralysis is in evidence. In morphology and development it resembles closely *T. evansi* and *T. brucei*. A similar disease has been noted in Venezuela and in Panama.

There is still some uncertainty about the differentiation between the several trypanosomiasis of horses. Some authorities claim that all of these, surra, nagana, mal de caderas, and dourine are one and the same disease and that the several trypanosomes which are connected with these manifestations are varieties of the same species and not different species. For instance, Koch, who worked especially with surra and nagana, believed these diseases and their parasites to be identical; on the other hand, Laveran and Mesnil find that there are constant morphologic differences between *T. brucei* and *T. equinum*; that animals immunized against nagana are still susceptible to mal de caderas. Most South American investigators believe that nagana and surra are identical, are in some doubt as to whether mal de caderas should be placed in this group or not, and are quite sure that dourine must be placed in a class by itself. While these matters are of scientific importance, to the epidemiologist the question of the agent or agents concerned in the transmission of horse trypanosomiasis is of greater importance. As has been stated, it has been quite conclusively shown that in South Africa *T. brucei*, the active agent in the causation of nagana, is distributed by a species of the tsetse fly, *G. morsitans*. In South America, Java, the Philippines, and India the tsetse fly is not in evidence; consequently, in these countries some other vector must be present. In India, South America, and the Philippines the economic loss from horse trypanosomiasis has been so great that even costly experimentation has been resorted to. Where valuable horses have been kept, all their food and their drinking water have been sterilized in order to prevent infection with the trypanosome. These measures have failed, as have all attempts to infect horses by inoculating their food with trypanosomes. It is well known that *T. lewisi* is transferred from rat to rat by means of fleas and, this being the case, it is highly probable that other species of trypanosomes might be transferred from rat to rat by the same agent. At one time it was suggested and widely believed that horses acquired their infection indirectly from rats. Infected rats were supposed to pollute with their excrement the grain and hay eaten by horses. There is, however, no reason for believing that the excrement of infected rats contains trypanosomes, and, in the second place, if trypanosomes should contaminate the food of horses only those horses would be in danger which had open wounds in the mucous membrane of the alimentary canal. It is quite certain that horse trypano-

somiasis is transmitted from animal to animal by flies. For the most part these are biting flies, such as the horse fly (*Stomoxys calcitrans*), and various species of tabanids. Nonbiting flies may transmit trypanosomes to open sores. In the epidemic of horse trypanosomiasis in the Philippines (1901-1903) Curry considered the *Stomoxys calcitrans* as the principal agent of transmission and found it feeding in great numbers on sick animals. Later in the same epidemic, Musgrave and Clegg confirmed these observations. Like observations have been made in Panama. Trypanosomes were detected in the stomachs and proboscides of horse flies up to 24 hours after they had been feeding upon diseased horses. Musgrave and Clegg summarize their extensive researches on the transmission of the virus in horse trypanosomiasis, as follows:

“Without going into further detail, there is an abundance of incontrovertible evidence that the disease is transmitted by a number of species of biting flies, as was the opinion of the natives of India and Africa long before science demonstrated the fact. It has thus far been conclusively shown that the tsetse fly (*Glossina morsitans*), at least one other variety of *Glossina*, *Stomoxys calcitrans*, *Musca brava* (?), *Taon*, and at least have one variety of *Tabani* transmit the disease. All other biting insects have been looked upon with suspicion, but absolute proof of transmission by them has not been furnished.”

T. equiperdum is the cause of a disease in horses, most frequently seen in India and North Africa, although occasionally found in Europe and North America. This disease is known as “dourine” or “mal du coit” and is transmitted not by an invertebrate host, but by coition between mare and stallion. It is, therefore, a venereal disease. Its incubation period is from 12 to 20 days. The first evidence is edema of the genital organs, which is generally painless and noninflammatory, although it may be accompanied by slight elevation of temperature. After a period of six or seven weeks there is an eruption under the skin of the sides and hind quarters, more rarely seen about the neck, shoulders, and thighs. This eruption is very variable in its appearance and continuance. It may be quite marked in the morning and completely disappear by night. Later there is marked emaciation and loss of strength. Superficial abscesses appear and do not heal. This is the usual course of the disease and is called “chronic dourine.” However, there is an acute type in which the animal after the first stage, as described above, dies from paralysis. The lesions found after death are most marked in the spinal cord and the lymphatic glands. In the former there is a gelatinous exudation, especially marked in the lumbar area.

T. dimorphon was discovered by Dutton and Todd as the cause of a disease in horses observed in various parts of Africa. More rarely it is found in cattle, goats, sheep, dogs, and pigs. In horses there is

first marked weakness, followed within from 14 to 21 days by fever. Gradually the animal becomes weaker, presents an appearance of marked illness and death results in about a year.

T. lewisi is a parasite found frequently in rats in this country. Apparently it has no ill effect upon its host. It is distributed among these animals by both lice and fleas. It serves a useful purpose in furnishing trypanosomes for laboratory study. Besides these trypanosomes, there are almost innumerable others which infest vertebrates of all kinds, including birds, reptiles, and mammals.

In 1903 Novy and McNeal made an epoch-making discovery which has contributed greatly to our knowledge of trypanosomes. These investigators, employing *T. lewisi* obtained from Ann Arbor rats, showed that these organisms can be grown in artificial cultures. They employed blood-agar tubes and obtained abundant growths, both in the incubator at 37° C. and at room temperature, the optimum being 25° C. Since that time, following the methods then employed, they and others have grown artificially many species of trypanosomes. This method has given the student of these parasites abundant opportunities to study not only their pathology, but their life-cycle. The same investigators have added materially to the list of species of trypanosomes. It is rather a serious, and certainly an interesting, question whether there is danger to man of infecting himself while working with these organisms, even though he confines himself to those which are believed to be nonpathogenic. Some years ago Lanfranchi, an Italian worker, became infected in some unknown way, presumably with surra trypanosome, with which, and nagana he had been carrying on some investigations. For about two years he had an occasional irregular fever, accompanied by debility and cutaneous edema. During this time, however, his mind remained perfectly clear. He was treated with atoxyl and tartar emetic and apparently fully recovered. Comparative studies which he made with the organism isolated from his blood showed that it was more closely related to *T. evansi* than to gambiense. This is the only instance, so far as we know, in which a trypanosome, presumably nonpathogenic to man, has been found in human blood. Recently, Macfie has reported a mild trypanosomiasis in a man in whose blood was found a trypanosome resembling *T. vivax*, hitherto believed to be incapable of infecting man. It may be added that Taute and Huber, convinced of the harmlessness to man of *T. brucei*, injected a large number of persons with trypanosomal blood of a horse without any ill effect. The latest information we have concerning trypanosomes comes from Turkestan, where in 1918 Yakimoff has reported trypanosomiasis among the camels of Turkestan and Astrakhan. Yakimoff has identified this parasite as *T. theileri*, although he thinks it probable that other species

may play a part. It is most probable that the world movements which have accompanied the Great War will be found to result in a wider distribution of trypanosomiasis, certainly among animals, if not among men.

Tsetse Fly.—We are at present interested only in *Glossina palpalis* and *G. morsitans*. Both species are confined, so far as we now know, to Africa and Arabia. They live naturally upon blood derived from land mammals, although it is reported that *G. palpalis* feeds upon crocodiles and hippopotami. Development of the young occurs to the larval state within the body, the female producing a single larva, followed by another after about two weeks. The unborn larva almost completely fills the abdomen of the mother. When extruded it is able to travel on its own account immediately and is found near the roots of banana plants. The motile period of the larva is of short duration, probably less than an hour. The larvae find a hole or some other hiding place about the roots of trees and develop into the imagos after passing through the pupal stage.

The adult fly is found most abundantly in the jungle near water courses. Bagshawe, who has studied these insects, has concluded that without aid they will transport themselves only for the short distance of about 80 yards, but they can be carried on animals, on boats, or other vehicles of transportation through long distances. They bite with most energy about midday and usually disappear late in the afternoon, to reappear about noon the next day. African explorers have found it desirable to protect themselves during the daytime and to locate their camps at least a quarter of a mile from water and jungle. As is the case with other insect-borne diseases, the area of distribution of the insect exceeds that of the disease; therefore, it is desirable that infected persons and cattle should not move into areas already infested by these flies and where the insects have remained free from the infection. When an infected individual passes outside the area of distribution of the fly he, of course, carries the disease with him but is not a source of danger to others.

Prophylaxis.—Human trypanosomiasis is now, and probably will continue to be for some years, on the increase in Africa. In that country the distribution of the carrying flies is much greater than that of the disease at present or at any time in the past. As traffic and opportunity develop in that country it is quite certain that the infection will sooner or later be coextensive with the habitat of the fly. The extermination of the fly will be a slow but constant process and sooner or later will be an accomplished fact. How many thousands and tens of thousands of lives will be destroyed before this is done depends upon the intelligence that is used in developing the interior of the African continent. In Africa it is quite certain that some wild animals carry

this virus, probably without harm or with but little harm to themselves. These act as reservoirs and keep up the supply of virus, which is transmitted from time to time to man and domestic animals. It seems that the flying range of the tsetse fly is not great and much can be done by cleaning out the jungle around villages and rendering access to drinking water easy without danger of being bitten by an infected fly. Travelers can protect themselves by selecting proper locations for camps and by protecting their persons from biting flies.

Protection against horse trypanosomiasis is a matter of marked economic importance. A country in which this disease does not exist should protect itself by placing such restrictions upon the importation of horses and other animals as may be necessary to prevent the introduction of the disease. All imported animals should be examined for the parasite and if found the animal should be killed and the body promptly and efficiently destroyed. During the epidemic in the Philippine Islands (1901-1903) the United States very promptly forbade the importation of any and all animals from these Islands. The danger is that some infected animal may find its way into the country from some port not known to be infested. Special attention should be given to the importation of wild animals for zoologic gardens, for circuses and other shows.

In a country in which horse trypanosomiasis has already been introduced the eradication of the disease is not so easy. It must be undertaken promptly, however, because the wider it spreads the more costly will be its extermination and the greater length of time will it require. In all cases sick animals must be promptly reported and when trypanosomiasis is diagnosed the animal must be killed or it must be isolated until properly treated and cured.

Arsphenamine and its congeners hold out great promise in the treatment of trypanosomiasis and it is more than probable that an effective and curative agent for this disease will be found in the near future that will be of great service in the eradication of the disease. In 1921 it was reported that expeditions were to be sent from both England and Germany to Africa with the purpose of testing out certain arsenical preparations in the treatment of trypanosomiasis.

A certain highly complex arsenical preparation known as tryparsamide (the sodium salt of N-phenylglycine-amide-p-arsonic acid) has already been demonstrated experimentally by Pearce and Brown to be effective in infected animals and has been tested to a limited extent on man.

Bibliography

- BRUCE, D.: Further Report on the Tsetse Fly Disease or Nagana in Zululand, London, 1897; appendix, 1903.
CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, sec. ed., New York, 1913, William Wood & Company.

- DUKE, H. L.: *Parasitology*, 1919, xi, 415.
- LAVERAN, A., AND MESNIL, F.: *Trypanosomes and Trypanosomiasis*, sec. ed., Paris, 1912.
- MCNEAL, W. J.: *Jour. Infect. Dis.*, 1904, i, 517.
- MUSGRAVE, W. E., AND CLEGG, M. T.: *Bull. No. 5*, Bureau of Government Laboratories, Manila, 1903.
- NOVY, F. G.: *Jour. Infect. Dis.*, 1906, iii, 394.
- NOVY, F. G., AND MCNEAL, W. J.: *Contributions to Medical Research*, Vaughan, 1903, 549; *Jour. Infect. Dis.*, 1904, i, 1; 1905, ii, 256.
- NOVY, F. G., MCNEAL, W. J., AND HARE, W.: *Jour. Am. Med. Assn.*, 1904, xlii, 1413.
- NOVY, F. G., MCNEAL, W. J., AND TORREY, W.: *Jour. Infect. Dis.*, 1907, iv, 223.
- Reports of the Sleeping Sickness Commission of the Royal Society, London, 1903-1908, Nos. 1-9.
- ROGERS, L.: *Fevers in the Tropics*, Oxford University Press, London, 1908.
- TODD AND WOLBACH: *Ann. Trop. Med. & Parasitol.*, v, 245.
- YAKIMOFF, W. L.: *Parasitology*, 1918, xi, 35.

CHAPTER XXV

FRAMBOESIA

Yaws (in English colonies); pian (in French colonies); boubas (in Brazil); parangi (in Ceylon); koko (in the Fiji Islands); gattoo (in West Africa); various other local names.

Description.—This is a chronic, infectious disease, characterized by indefinite prodromal symptoms, with development of a primary sore and followed by a granulomatous fungous eruption, due to a specific spirochete discovered by Castellani and designated by him as *Treponema pertenue*. In many respects this disease resembles syphilis, inasmuch as there are at least three fairly well-marked stages in its progress. The period of incubation, including the appearance of the primary sore, is highly variable, as determined by the study of its natural development and by observations after experimental inoculation. The time required for the progress of this stage is generally placed in cases of natural infection at from two to three weeks, but in many instances it is probably much longer, since it has been observed after inoculation that some months may elapse before disturbance of health functions rises to the plane of clinical recognition. Rat makes the following statement:

“There are no special symptoms to be recorded in connection with the incubation stage. Being unaware of the changes taking place in his system the patient takes no note of any derangement of his health which may occur during this period, or, should he do so, attributes it to an incipient catarrh, or malarial fever, or to disordered digestion. While the little attention paid to such deviations from health makes it most probable that the suggestive symptoms, in cases of ordinary infection, can only be trifling, it is impossible to suppose that a disease which is capable of affecting the system so profoundly can occupy it for several weeks without inducing considerable changes in one or more of its tissues. In cases of inoculation which have come under my notice, the following symptoms were observed. The skin is dry; its papulae are unusually prominent; there is a loss of pigment in certain portions of the skin at different parts of the body, but chiefly in the neighborhood of the site of inoculation, producing light colored patches of variable size which appear yellow in the African; and the upper cells of the epidermis become dry, causing the latter to shrivel, and giving the patient's skin the appearance of being irregularly encrusted with salt. This condition, presumably due to atrophic changes induced through nervous agencies, is probably always present in a greater or less degree; but, as it is sometimes limited to only a small surface around the infected point, it may escape notice. It is often, however, a very prominent symptom which persists, in some cases, long after the eruptive stage, as an indication of the imperfect development of the disease or of its latency in the system. Palpitation of the heart is readily induced during this stage, whenever the patient exerts himself, especially when climbing, or when mentally excited. There is, also, giddiness, chiefly after arising from a stooping

posture. Edema of the limbs and eyelids is sometimes present. These are indications of the anemia produced by the disease, and manifesting itself under the microscope by an abnormal preponderance of white-blood corpuscles."

Many observers report the most prominent prodromal symptoms as consisting of an irregular fever, accompanied by rheumatic pains, headache, and general malaise. Usually, after these indefinite symptoms have continued for two or three weeks, the primary sore comes into evidence. There are authorities who assert that there is not in all cases a definite, well-defined characteristic primary sore, but the best opinion upon this matter is that expressed by Rat and confirmed by many others, that a primary lesion in yaws is quite as characteristic of that affection as the chancre of syphilis. As in the last-mentioned disease, there may be difficulty in detecting the initial lesion. Especially is this true among those already suffering from some eruptive disease, and even among those whose lack of bodily cleanliness may make the detection of a specific pimple difficult. In others, the primary sore may be located in a previously existing lesion in the cutaneous tissue; indeed, such lesions give opportunity for the penetration into the body by the specific organism of yaws. Rat gives the following description of the primary sore:

"When fully developed, the initial cutaneous lesion of yaws consists of a papule which, at the end of about seven days, develops a pale yellow fluid at its apical third. After about seven days more, the fluid dries, and on the removal of the scab thus formed, an ulcer is revealed, with perpendicular edges and a clean base lined with granulation tissue. In the course of the following fortnight, the ulcer heals by contraction from the circumference to the center, leaving a very slight superficial cicatrix lighter at first in color than the adjacent skin, but gradually assuming the complexion of the patient. The ulcer may last two months before healing of itself. Occasionally the papule disappears entirely by ulceration of its substance, a circular, or elliptical clean shallow sore being formed which may attain the size of a florin and heals by granulation. Another form sometimes assumed by this lesion is that of a subcutaneous tubercle which does not generally proceed to ulceration, but disappears by absorption during which the epithelium on its surface perishes and forms a thin white scale. Occasionally the papule is deep-seated and becomes large enough to be considered a subcutaneous tubercle. In course of time, a pustule forms over it, which, on rupture, reveals several minute orifices in the skin through which the subjacent pus escapes."

In certain endemic areas the natives have in their various tongues some name for the primary sore which, in all cases being translated into English, means "mother yaw." The primary sore is usually extragenital. On men and children its most common location is on the exposed parts of the body—hands, arms, feet, and legs; although it may be anywhere. In nursing women infected by their infants, mother yaw is most frequently on the breast. Castellani reports that in Ceylon a frequent site on the mother is just above the hip, due to the custom there prevalent of carrying the child astride the mother's hips. The primary

sore is never indurated, as is that of syphilis, and while the lymphatic glands in the neighborhood may for a time be slightly enlarged and moderately painful, they never suppurate. The continuance of the primary sore is variable, usually extending from two or three weeks to as many months. Finally it heals, leaving a whitish scar, which, in time, becomes more or less pigmented. Among the natives in certain endemic areas it is the custom to cauterize or otherwise roughly attempt to destroy the primary sore. As a result of these crude methods, ugly and deep wounds are inflicted, and in their healing more or less deformity may result. In some instances there is marked pruritus around the primary sore, and this leads to auto-inoculation as a result of scratching, in consequence of which there may be a bunch of papules, but, as a rule, these coalesce, forming a single large one.

The second or granulomatous stage usually comes into evidence about two weeks after the disappearance of the primary lesion, although the latter may continue during the secondary stage. In a typical case, about two weeks after the primary sore has healed, secondary symptoms, marked by an irregular fever, and accompanied by muscular and articular pains make themselves manifest. There is a daily rigor, followed by elevation of temperature, but not by sweating, as is the case in malaria. These general disturbances are accompanied by visible evidences of changes in the skin, which becomes dry, harsh, and furfuraceous. Concerning the general eruption of the secondary stage, Rat makes the following statement:

“On its first appearance, in a typical case, such as is often seen in a healthy child in Africa, the secondary eruption is not unlike lichen tropicus, the patient being covered from head to foot with minute red spots, and the skin presenting the appearance of having been irritated by long continued excessive perspiration. The rash begins on the head and develops from above downwards. The scalp is very slightly affected. At the end of the third day, the body is completely covered with the red spots. From their first appearance, the spots have been becoming more prominent, and about the fourth day, some of those over the head and face are sufficiently large to be described as conical papules, while those on the body and limbs attain similar proportions during the fifth and sixth days. The greater portion of the rash begins to fade after the third day, only a comparatively small number of the red spots developing into papules. The percentage of those which become papules varies considerably; and their number depends on the patient's previous and actual physical and mental condition and surroundings. Debility or a concomitant constitutional disease may interfere with the proper development of the eruption, which may also be retarded or almost entirely suppressed by exposure to cold or mental shock. On the seventh day from the first appearance of the secondary eruption, the apical third of the papule begins to acquire a pale yellow tint. This change is first seen in the papules on the head and proceeds downwards, becoming general and complete at the end of the ninth day. The alteration in color is not due to the presence of lymph or pus, but to a substance apparently in no way different from the inspissated secretion of the sebaceous follicles. The appearance thus produced on a black skin is very singular, and gives the idea of a

number of minute pieces of yellow wax, about the size of a small pin's head, having been stuck on, at intervals, over the patient's body. The next step in the progress of the eruption is the development of the papules into tubercles. The papule gradually expands and assumes a cylindrical shape. The pale yellow substance at the upper third, enlarges also in proportion, becomes dome-shaped, and gradually thickens until it assumes the appearance of a thick yellow crust, like that of eczema. An average tubercle when fully developed, measures a quarter of an inch in diameter and an eighth of an inch in height. When the crust is removed from its summit, a mass of granulation tissue is seen covered with a creamy secretion. It was to allow of the passage of this granulation tissue that the papule expanded in the way above described. The crust is formed by inspissation of the creamy secretion which adheres, as it thickens, to the sides and undersurface of the pale yellow substance at the apex of the papule. Whenever removed, the crust is reformed by this secretion from the granulation tissue of the tubercle; and, when the discharge is abundant, the excess exudes as a pale yellow fluid from beneath the crust."

While the above is an accurate description of the development of the secondary stage in a typical case of yaws, there are many variations; the tubercles varying greatly in number, in size, in depth of penetration, and in the resulting destruction of tissue. This is to some extent dependent upon the location of the tubercles. When they appear in the palms of the hands or on the soles of the feet, the callous tissue covering the ulcers offers great resistance to penetration; consequently, the ulcerative processes continue to extend subcutaneously, resulting in wide and deep destruction of tissue. A single ulcer on the sole of the foot may form a deep cavern covering a large area before the callous skin cracks, breaks, and permits the escape of the products of ulceration. Ulcers may form under the nails, leading to degenerative changes in these tissues, and occasionally in their complete destruction. Ulcers between the toes and fingers are likely to harbor streptococcic guests and these aid in the destruction of tissue and modify the ulcerative processes. Cases of this kind may give off a fetid, disgusting odor, which, however, may be arrested by treatment of the ulcers with proper germicidal agents which kill the streptococcic invaders but have no effect upon the specific virus of yaws. In some instances instead of a single crop of tubercles, successive eruptions may come and go. While those on one part of the body may be healing and disappearing, a new crop may occur somewhere else. It is an interesting observation that an intercurrent exanthematous disease, such as variola or measles, may for the time being check the development of the eruption of yaws, but when the intercurrent disease has passed, the manifestations of the yaws infection proceed in their natural way; on the other hand, there are certain diseases, especially tuberculosis and syphilis, which greatly intensify the effects of the yaws eruption and prolong its continuance. Poor food, overcrowding, and filthy surroundings have a like effect. The normal end of the granulomatous eruptions in yaws is brought about by

interstitial absorption, and this usually requires about six weeks, though a much longer time may be necessary. The secondary lesions rarely extend to the mucous membranes, although a granulomatous ulcer occasionally appears in the nose. There is in certain of the West Indies, in Guam, in the Caroline and Fiji Islands, a severe ulcerous disease, which generally begins on the soft palate, spreads to adjacent parts, and is destructive to all tissues, including cartilage and bone. This disease is known as gangosa and it has been variously classified as leprosy, syphilis, tuberculosis, and yaws. The weight of opinion, however, is that it is a disease *sui generis*. The blood serum in this, as well as in yaws and in trypanosomiasis, gives a positive Wassermann reaction. If it be a form of yaws it belongs to the tertiary rather than to the secondary stage.

In severe forms of the granulomatous eruption in yaws, muscular tissue may suffer more or less from the ulcerative process and there may be resulting contractures; indeed, the granulomatous ulcer may penetrate the periosteum, and in rare instances the bony tissue may be involved.

While many cases of yaws terminate favorably with the close of the secondary stage, there are patients with this disease, especially those suffering from any constitutional debility or in the absence of proper food, in whom the disease process extends to the tertiary stage, thus making more marked the similarity between this disease and syphilis. Of the tertiary stage, Rat writes:

“The most characteristic ulcers of this period are those originating in dome-shaped subcutaneous nodules, which are similar in appearance to the gummata of syphilis, and vary from a quarter of an inch to an inch in diameter. These are generally situated over the instep and about the ankle and most commonly over the external malleolus, though they may be met with over any part of the leg below the knee. They also occasionally occur on the upper limb, in situations corresponding to their usual sites on the lower one. * * * They resemble cysts in outward appearance, but they are found on manipulation to be less circumscribed and movable and more intimately connected with the surrounding tissues. Though not as firm as a fibrous tumor, they are not doughy like a lipoma, but convey to the touch the impression which might be expected from a subcutaneous mass of granulation tissue firmly and broadly based upon the deeper tissues. They are perfectly painless before they ulcerate, and they may remain unchanged for a period varying from a month to a year or more. At the end of an uncertain time, the skin over the nodule becomes red and tender, softens and ulcerates from the center towards the circumference, the granulation tissue beneath being thus gradually revealed. The latter is then seen undergoing a softening process and discharging a fluid similar in all respects to blood-stained serum. By the disintegration of the nodule, a clean ulcer, of the same diameter as the latter and about half an inch in depth, is produced, with a granulating base and perpendicular or undermined edges. Such an ulcer generally lasts from three to four months, but may persist for a year or more or may become chronic and incurable. Healing proceeds from the circumference towards the center, the edges subsiding and contracting and finally uniting and bridging over the cavity formed by the destruction of the nodule. Over the de-

pression thus left the epidermis perishes, while, beneath it, fresh tissue grows towards the surface and raises the skin to its former level. The scar left is small compared with the size of the nodule and is very slightly lighter in color than the surrounding skin.”

In the tertiary stage the lesions may involve not only the cutaneous tissue, but mucous membranes, the muscles, and the bones. Whether the central nervous system becomes involved in the tertiary stage is a matter not definitely settled. Castellani and Chalmers say:

“Tertiary affections of the internal organs and of the central nervous system seem to be rare.”

History.—The early history of framboesia is obscure. We have elsewhere referred to the fact that the disease described by the writers of the Old Testament under the name of leprosy, probably included many disfiguring and unsightly cutaneous sores. In his medical essays, written in 1744, Hume, of Edinburgh, argues that the disease which afflicted the Hebrew children and which is described in the thirteenth chapter of Leviticus, may have been yaws. Later this idea was supported by Adams in his “Observations on Morbid Poisons.” Arabian writers of the ninth and tenth centuries, especially Abbas and Avicenna, wrote of a disease under the name of “safat” or “sahafati,” which may have been either syphilis or yaws. That it was the latter is believed by Hillary, who studied yaws in the West Indies during the eighteenth century and called attention to its resemblance to the Arabian leprosy discussed by the writers mentioned above. More definite information begins after the discovery of America. In his work on the General and Natural History of the Indies, first published in 1526, Oviedo y Valdez reported his observations among the natives of San Domingo and gives an account of a disease which could hardly have been any other than yaws. This authority states that the disease was known under the Spanish name of “bubas,” which from that time down to the present has been used in South America, and especially in Brazil, to designate cutaneous sores and includes yaws, cutaneous leishmaniasis, and possibly other diseases. In his work on the diseases of Brazil (1648) Pison described the same disease and in 1658 Rocheford, in his Natural and Moral History of the Antilles of America, makes the following statement:

“The bad food, consisting of crabs and other insects on which the Caribs live is the reason why they are almost all subject to a serious complaint which they call pyans in their language, as the French are to the smallpox.”

In 1665 Breton spoke as follows of a disease known to the Caribs by the name “yáya”:

“This is an indigenous disease which prevails as commonly in the Islands as the great pox in France and of which the savages cure themselves without trouble and risk. * * * It is but slightly dangerous, though very common amongst them.”

In his book entitled, "New Voyages to the Islands of America" (1694) Labat says:

"The Caribs are very subject to l'espian. It must be confessed that this disease is peculiar to America and that it is indigenous there; all who are born there, blacks or Caribs, of whatever sex they may be, are attacked by it almost at birth, though their fathers, their mothers, and their nurses may be quite healthy, or at least may appear so."

It was believed for a while that this disease is confined to the Western Hemisphere, but in 1718 Bontius called attention to the fact that it was widely distributed and indigenous in the Dutch East Indies. Labat was the first author to call attention to the close resemblance between and the possible identity of yaws and syphilis, and suggested that the disease which apparently originated among Spanish soldiers and soon spread throughout the armies in Naples in 1493 and then widely scattered through Europe and which is believed to have been syphilis, might have been yaws. We shall discuss the nature of the Neapolitan disease in the chapter on venereal diseases.

There is evidence that a disease or diseases resembling yaws have appeared in epidemic form even in northern Europe and in Canada in the past. About the end of the seventeenth century an eruptive disease, the lesions of which had a resemblance to raspberries, and known as sibbens or swins from the word "swin" (Celtic for raspberry) appeared in the west of Scotland, having been brought as was believed, according to Rat, by Cromwell's soldiers, or, according to Castellani and Chalmers, by sailors on a vessel from the West Indies wrecked on the Scottish Coast. A little later a similar disease, known as "button scurvy," appeared in Ireland and served as a basis for numerous articles by Irish physicians. Hirsch gives the following description of the clinical characteristics of button scurvy:

"Having been usually preceded for a longer or shorter period by an intense itching of the skin, coming on particularly at night, the disease is ushered in by an outbreak of small round spots, which gradually raise themselves above the skin and grow into tumors in size from a pea to a nut. The color of these tumors is at first dark red but becomes paler, the epidermis over them becoming at the same time thinner and thinner, and finally disappearing altogether; a granulating surface now protrudes and secretes a serous fluid, which becomes a dry crust on the summit of the tumor, and is quickly reproduced if it be taken off. The exerescence is elastic to the feel, and somewhat painful on pressure; the skin around it shows no kind of morbid alteration. The number of such nodules in the same person varies from one to fifty, or even more. The favorite seats of the exanthem are the palms of the hands, and the inner sides of the thighs and arms, more rarely the hairy scalp, and sometimes even the scrotum and perineum, where it might be very easily mistaken for condylomata. When the tumors have lasted sometime they begin to shrivel, the scabs fall off, and disclose a red spot, which shortly assumes the normal color of the skin. Only in the event of suppurative disintegration of the tumors, which seems to be on the whole rare, is there a cicatrix

formed in the skin. The duration of the malady is usually many months, and it appears to depend as much upon the long persistence of individual nodules as upon recurrences. It is only the exhaustion following a very copiously developed exanthem or one of long persistence that makes button scurvy dangerous to the health or life; in the great majority of cases the general well-being appears to have been in no wise affected, and symptoms of constitutional disturbance were never observed. Concerning the anatomical structure of the tumors Wade, Corrigan, and Kelly agree in saying that they should be considered as hypertrophic growths of the papillae of the corium."

For some years button scurvy prevailed in true endemic form in the southern counties of Ireland, and its infectious nature seems to have been well recognized. It was believed to be disseminated by contact, and clothing worn by infected persons was regarded as a dangerous carrier of the infection. Wallace found it frequent among those who handled clothing either in laundry work or in traffic in these articles. Kelly observed it most frequently among those engaged in caring for flocks of sheep infected with scabs, and came to the conclusion that the disease was transmitted from sheep to man.

Early in the eighteenth century a similar disease appeared in Sweden and Norway and thence spread eastward to Finland and southward to Denmark and Holstein. This disease was known under the Scandinavian name of "radesyge" and was described by Sorrensens as follows:

"Pains in the head and limbs, especially during the night; herpetic eruptions on the forehead, chest, shoulders, and arms; slight inflammation of the throat. The herpetic eruption becomes more extensive, and acquires a raised margin. It shows itself on the face, in patches, at first superficial, which gradually become deeper; subcutaneous tubercles are formed, which pass into a state of inflammation and suppuration. The inflammation of the throat increases; there is ulceration of the uvula and tonsils, which extends to the pharynx; similar ulcers appear in the region of the palate; the palate bones are attacked and destroyed. On the limbs appear ulcerations with dark red edges, sometimes covered with a thick dry crust. On the genitals, anus, and perineum are developed condylomata and excrescences which extend to the thighs. The disease attacks the septum of the nose, which ulcerates and becomes perforated; there is caries of the osseous system, especially of the bones of the nose, the long bones, and the frontal bones; tophus and exostoses are observed, which soon change to caries. The primary cause of the disease is unknown; all that is known is that a *contagium* is developed which is communicable by means of the saliva, the perspiration and ichor, knives, spoons, and clothes, as well as by contact. Mercurey is the first and most important of all the remedies for it."

In 1710 there was an epidemic of a similar disease on the shores of Lake Huron, which, under the name "mal de chicot," spread among the halfbreeds and Indians. In all these localities these eruptive epidemics prevailed for a few years—in some places only for a few months, and then disappeared. It will probably be impossible to ever determine their nature, but it is not at all likely that they were due to the specific microorganism which we now know as the cause of framboesia.

Lancereaux has the following to say concerning the Canadian epidemic:

“This disease, which made rapid and extensive progress amongst the Canadians in a few years, began to show itself in 1760 amongst the natives of the banks of Lake Huron. In 1780 it appeared amongst the inhabitants of the shores of St. Paul’s Bay, and in a few years spread over a great part of Canada, committed great ravages amongst some of the Indian tribes, and chiefly amongst the Ottawa Indians. In 1785, 5,800 individuals were known to be suffering from this disease in Canada, without counting those who did not give notice of their being affected; it was still unknown at that time, however, to all the neighboring Indians. It commenced, according to Swediaur, by small pustules on the lips, the tongue, the interior of the mouth, and more rarely on the genital organs. These pustules, which at first resembled small aphthae, filled with a whitish puriform fluid, were so many germs of transmission. The matter contained in them was so virulent, that it infected those who ate with the same spoons, or drank from the same vessels, or smoked the same pipes. It was even observed to be communicated by the bed-linen, clothes, etc. The disease was afterwards characterized by considerable deposits (tubercles), nocturnal pains in the bones, ulcers of the mouth and throat, complicated affections of the glands, sometimes suppurating, most frequently hard and indolent. Finally, the bones of the nose, the palate, the cranium, etc., became carious; the hair fell off, pains in the chest, cough, loss of appetite, etc., supervened, which announced the approach of death. Both sexes and all ages were equally liable to the disease; children suffered in great numbers.”

In 1578 a pustular disease appeared among the inhabitants of Brünn in Moravia, which is described by Jordan as follows:

“This epidemic, without being very fatal, was accompanied by most alarming symptoms. In less than two or three months, 180 persons were attacked by it in the town or suburbs, and many of the country people were equally affected. The cause of it was attributed to the waters of the baths, the inhabitants being in the habit of bathing on a certain day and of having blood drawn by cupping, and it was believed to have commenced on Saint Luce’s Day, a festival celebrated with pomp in the town. Those who had bathed and been cupped on that day were observed to have contracted it. It did not become developed, however, until one or two weeks, or even a month, after that period. The Senate caused the bathing establishment to be closed, and the disease, which had become mitigated during the winter, disappeared towards the vernal equinox. After a certain period of unusual lassitude, inflammation and sanious ulcers appeared on the places where the cupping-glasses had been applied. It was a singular circumstance that, notwithstanding the great number of cupping-glasses applied, one or two only became the seat of ulcerations. In some, the whole body was afterwards covered with pustules, which rendered the face deformed and horrible. During the progress of the disease, callosities supervened upon the head, which, on bursting, discharged a viscous fluid, like turpentine. Severe pains were then felt in the arms, shoulders, lower extremities, and especially in the tibiae, where those bones are covered by periosteum only. The pains increased at night and diminished in the morning. Next followed prostration of strength, stupidity, and even mental aberration. A fetid discharge flowed from the nostrils, the appetite was lost, and the patients wished for solitude. Bitters, decoction of guaiacum, and turbith mineral were the chief remedies employed; the ulcers were dressed with mercurial ointment.”

In 1718 Bontius described an epidemic disease which prevailed at that time on the Island of Amboyna. It is stated that this disease resembled syphilis, but was transmitted quite independently of sexual intercourse. It is now certain that this was yaws.

Boyer has described an epidemic which occurred in Saint Euphemia in 1727. It seems that a midwife had on her index finger of the right hand a pustule which caused considerable itching. This infection was transmitted to the children of more than fifty women whom she delivered or examined. A surgeon found on the vulva of several of these women ulcers of the same nature. In the meantime, the disease spread to the children whom their mothers were suckling and to the husbands to such an extent that in four months more than eighty persons were found to be infected. The bodies of those affected became covered with pustules and ulcers, which were believed to resemble the conditions characteristic of the epidemic of syphilis in the latter part of the fifteenth and the early part of the sixteenth centuries in Europe.

A similar epidemic was reported by Raulin as occurring in Nérac (a town in southwestern France) in 1751. Apparently, this epidemic originated from a wet nurse. Other nurses became affected and within a year, more than forty women and children, besides several men, were afflicted with this disease.

In 1786 Falcado reported an epidemic in several villages in Tyrol, where it continued for some years and did not entirely disappear until 1814. It was believed that the disease was imported by a beggar-woman suffering from venereal itch, warts, and ulcers on the genitals. This distemper was found to be amenable to mercurial treatment.

In 1800 Grobniek and others reported the existence in villages near Fiume of a disease which was characterized by malignant pustules on the face and other parts of the body, leading to caries of the bones, destruction of the tongue and ears, and ulceration of the genital organs. It was believed that this disease was brought in 1790 to Scherlievo, a village a few miles from Fiume, by four sailors who came with women from the banks of the Danube after the war against the Turks.

In the early part of the nineteenth century an epidemic disease, accompanied by pustular eruptions, with tubercles about the anus and genitals, was reported in several villages in southern France, especially in Haute-Saône.

Lancereaux, in our opinion upon insufficient evidence, cites the above local epidemics as illustrations of epidemic syphilis corresponding, on a small scale, with the great epidemic of this disease which appeared simultaneously with the invasion of Italy by Charles VIII of France in 1494.

While there seems to be no doubt that framboesia existed in at least some of the West Indian Islands at the time of their discovery by Columbus, it is also quite certain that it existed in Africa at the same time, that the negroes imported from Africa into the West Indies and into parts of North and South America were infected with this disease

in their native land, suffered from it during their voyages, continued to bear the infection, and disseminated it in their homes in the new world. On the plantations on the British West Indian Islands, so long as slavery existed in these, yaws was recognized as an ever-present and an infectious disease. In some of these localities, yaws houses or places for the segregation of the bearers of this disease were provided for on nearly every estate. Through this means it was claimed that on certain islands, notably Barbados and Antigua, the disease was completely eradicated. When slavery was abolished in the British West Indies (1838) this agency in the restriction of the disease was discontinued and in some localities at least, the disease became widely scattered. The result was an alarming increase in its prevalence in most of the islands, and it again became the custom to provide yaws houses. These, however, have not proved so effective as they did before emancipation, on account of the greater difficulty met with in the early detection and prompt isolation of the cases.

In 1848 Paulet inoculated 14 negroes with material taken from granulosomatous ulcers and developed yaws in all, after an incubation period which varied from 12 to 20 days. In 10 of these cases the initial sore was at the point of inoculation, while in others it was elsewhere. In 1882 Charlouis, a Dutch physician in the East Indies, made a large number of inoculation experiments, from which he deduced the following conclusions:

“(1) Framboesia is a contagious disease; (2) it is both auto- and hetero-inoculable; (3) it may attack the same person more than once; (4) patients with framboesia, who are inoculated with material from themselves or others, develop, at the seat of inoculation, either an ulcer (resembling an *ulcus molle*) or a fungating tubercle; and that on the other hand such inoculations do not exert the slightest influence upon the pre-existent disease; (5) both the secretion and blood from a tubercle are infectious, and the results of inoculation with both are identical; (6) the virus is a fixed contagium and infection can therefore only result from actual contact; (7) the products obtained from tubercles in the stage of aggravation and of full development are infective; and as soon as they begin to dry up infection is no longer possible; (8) the period of incubation may last from three to five months; (9) fever, accompanied by gastric disturbance, and pain in the bones precedes the eruption and may be concurrent with it for a time; (10) if the framboesia be not of long standing the spot by which the virus entered the body can usually be approximately determined, since glands corresponding to this situation are specially enlarged.”

The same investigator pointed out the clinical resemblances and differences between framboesia and syphilis and settled positively the question of the identity or nonidentity of these diseases by showing, in the first place, that framboesia is auto-inoculable, while syphilis is not, and in the second place, having syphilis does not protect from framboesia, and having framboesia does not protect from syphilis.

It is worthy of note at this place that the question of auto-infection in yaws has not been settled with entire and clear-cut satisfaction. As we have just stated, Charlouis reported this disease as auto-inoculable. On this point Rat wrote in 1891, as follows:

“The question of auto-infection is an important one, inasmuch as it would afford plausible explanation of the dissemination of the disease over the rest of the body from a single infected spot, as has been suggested by Leloir and Vidal in the case of Delhi boil. But my experience leads me to believe that auto-infection seldom, if ever, occurs in yaws. All the attempts which I have made to inoculate a patient with yaws virus from tubercles on his own body or from more recent or more advanced cases, have failed; nor have I ever known a case in which an eruption has been caused by virus conveyed by the patient himself from one part of the body to another. There are many instances where only one tubercle has developed and has persisted for months in careless and uncleanly patients, without any subsequent extension of the skin lesions. A tubercle frequently develops on the skin near the margin of the anus, and persists, as a result of constant irritation, long after the other tubercles have disappeared; but it never produces another on the opposite spot with which it is constantly in contact. To test whether an abrasion under these circumstances would induce infection, I have excoriated the skin on the opposite side, but, even then no tubercle was produced at the site of abrasion. It is certainly not by auto-infection that the development of yaws tubercles under the thickened epidermis of the palms and soles of the negro can be explained. It is possible that auto-infection may occur during the early period of the primary yaws lesion; but persistent unilateral tubercles of the buttocks are found so frequently that one cannot but conclude that auto-infection is not a consequence of contact with the secondary yaws tubercle. There are doubtless cases in which two tubercles are found on the buttocks exactly opposite to each other and very suggestive of auto-infection, but the probabilities in such cases are that the tubercles arose independently of one another as they often do at the corners of the mouth.”

Within recent years numerous investigators in the East Indies and in Ceylon have made many inoculation experiments on different species of monkeys. In Java, Neisser, Halberstadter, and Prowazek found that the native monkeys of that region when inoculated with material taken from yaws, pass through a period of incubation which varies from 16 to 92 days, and develop a primary sore at the point of inoculation. In some species there is secondary and multiple eruption, while in monkeys belonging to the genus *Macacus* there is only one sore and that at the point of inoculation. That the infection, however, is general is shown by the detection of *T. pertenuis* in the spleen, in certain lymphatic glands and occasionally in other tissue. Rather rarely it happens that peripheral blood is successful in producing a local lesion, or any other positive evidence of infection. The cerebrospinal fluid at all stages of the disease seems to be free from the infecting agent and attempts to inoculate animals with it have always failed. Castellani, in Ceylon, has demonstrated that monkeys inoculated with framboesia are not immune to syphilis and, vice versa, that those inoculated with syphilis are not immune to framboesia. The experience of Levaditi has been somewhat

different. He reports that monkeys immunized against yaws acquire no immunity to syphilis, but that monkeys immunized against syphilis acquire a partial immunity against yaws. Ashburn and Craig, experimenting upon Philippine monkeys, find that these animals are susceptible to framboesia, but not to syphilis.

In 1905 Castellani discovered in smears made from the papules, *T. pertenue*, which is now accepted as the specific cause of this disease and a description of which will be given later.

In 1891 Rat, who had had wide experience with yaws in the West Indies, South America, and Africa, wrote a report on this disease, which contains, chronologically arranged, all the literature up to that time, and which has become the basic classical treatise on the subject.

As was first shown by Nichols, arsphenamine is of great value in the treatment of framboesia. On this point Castellani and Chalmers make the following statement:

“The most efficacious and quickest treatment is by Ehrlich-Hata salvarsan or neosalvarsan, while potassium iodid and tartar emetic are fairly efficacious, and mercury practically useless. Salvarsan and neosalvarsan and their substitutes seem to act in framboesia more quickly and more powerfully than in any other spirochetal and treponemal condition; in fact, in framboesia the *therapia sterilisans magna* in Ehrlich’s meaning, by a single dose, can at times be obtained. Salvarsan was first tried with good results in experimental yaws by Nichols, and, in patients suffering from the disease, by Strong in the Philippine Islands, and Castellani in Ceylon, while Alston in the West Indies made the interesting observation that the serum of patients treated with salvarsan showed remarkable curative powers when injected in framboesia patients. Recently the salvarsan treatment of framboesia has become general, having been used with very good results by DeGorge and Mouzels, Sabella, Born and many others. The salvarsan treatment is especially efficacious in recent cases. Relapses, however, occasionally occur. In very old cases with tertiary lesions the treatment may fail. At the present time neosalvarsan, instead of salvarsan, is generally used.”

In closing the history of framboesia it may be interesting to note that many of the local designations of this disease are used because of the resemblance of the eruptions to certain berries, especially raspberries and strawberries. It was this which led Sauvages to propose the name framboesia, from the French word “framboise,” meaning raspberry. In some respects the selection of this name has been unfortunate. In the first place, every disease, the eruptions of which have a real or a fancied resemblance to raspberries, has been designated as framboesia. This has led to the inclusion under this term, of diseases of various origin, nature and symptoms; on the other hand, the term is not in all cases applicable to the disease. On this point Rat makes the following statement:

“The name ‘framboesia,’ manufactured from the French *framboise*, was given by Sauvages in 1761 to the disease, from the fancied resemblance of the tubercle to a

raspberry. It would be difficult, however, to imagine anything more unlike raspberries than a crop of yaws tubercles covered with their thick yellow crusts. In cases in which there is but little anemia the tubercle on removal of its scab, is exactly like proud flesh covered with a creamy fluid, and in these the term 'framboesia' may be considered appropriate; but, as in the majority of instances, there is considerable anemia, and in all, the tubercle becomes gradually paler, what is usually seen when the scab is removed, is a lump of fawn-colored tissue which becomes lighter in color as the disease advances. In old standing cases the granulation tissue becomes bloodless and white like cartilage. With their yellow crusts slightly raised above the skin, the tubercles are remarkably like the tops of a cauliflower which has become yellow from being kept in pickle. If an eighth of an inch were pared off the top of a pickled cauliflower and pieces of it a quarter of an inch in diameter, were stuck on a person's face at distances of an inch apart, a very fair representation would be obtained of a crop of yaws in full bloom. Sometimes, however, the crusts have a more even surface than that of a cauliflower, and resemble yellow wax or amber."

Geographical Distribution.—Framboesia is widely distributed throughout the tropical belt around the world. In tropical Africa, especially along the coast, it is common, and some of the writers on the history of this disease would have us believe that this was its original home and that it was transported from tropical Africa to the West Indies when the slave trade was in existence; but if it be true that Oviedo y Valdez saw it in San Domingo before 1526, it must have been indigenous on that Island, or at least it could not have been brought there by slaves from Africa. It is found throughout the Dutch East Indies and the Malay States. Again, it may be stated that it was not carried to the East Indies by the importation of African slaves, since it was reported in Java by Bontius as early as 1718 and before there had been any such importation. The truth seems to be that framboesia is indigenous alike in tropical Africa, in the East and West Indies, and in many islands in the Pacific. There is some difference of statement concerning its presence in India, although, according to Powell, it is found in Assam. Manson states that yaws is rare in China, especially on the coast. In the Fiji Islands it is so common that, according to Daniels, parents are in the habit of inoculating their children with it, thinking that it is inevitable and that it is wise to select the time the child shall have it. In Brazil it is common, but it is difficult to make any statement concerning its relative prevalence in that country, because it has been confounded with cutaneous leishmaniasis and with blastomycosis, all these eruptions going under the common name of "boubas" or "bubas." In some of the West India Islands, framboesia has prevailed so extensively that repressive measures have been resorted to and segregation has been spasmodically carried out with satisfactory results when properly done. In a British Colonial report on this disease in Trinidad in 1902, it is said that at that time both yaws dispensaries and yaws hospitals were in operation and that not less than 1,751 cases were under

treatment during the year. While yaws seems to be scattered around the world in tropical and subtropical countries, apparently it does not extend to high altitudes even in these regions. There has been considerable stress placed upon the relative geographical distribution of yaws and syphilis. Syphilis seems to be about the same in all climes at all altitudes and under all terrestrial temperatures. However, one meets with some rather interesting things in the study of the geographical distribution of these two diseases. It is the testimony of all medical men who have studied the diseases of the Fiji Islands that among the natives, syphilis is practically unknown, while framboesia is, as we have just stated, so common that parents regard it as inevitable. Turner makes the statement that syphilis was unknown in Samoa up to 1880, while framboesia has been prevalent from the earliest discovery of this group of Islands, and in all probability much longer. In some of the British possessions in the West Indies, framboesia has been exterminated, while syphilis continues.

Is framboesia indigenous in the United States? Wood has collected evidence bearing upon this subject. In 1737 Brickell published his "Natural History of North Carolina, with an account of the Trades, Manners and Customs of the Christian and Indian Inhabitants." Wood quotes from this work the following:

"The yaws are a disorder not well known in Europe, but very common and familiar here; it is like the lues venera, having most of the symptoms that attend the pox, such as nocturnal pains, Botches, foul Eruptions, and Ulcers in several parts of the Body, and is acquired after the same manner as the pox is, viz., by copulation, etc., but is never attended with a gonorrhea in the beginning. This distemper was brought hither by the negroes from Guinea, where it is a common distemper among them and is communicated to several of the Europeans or Christians by their cohabiting with the blacks, by which means it is hereditary in many families in Carolina, and by it some have lost their palates and noses."

Wood is inclined to accept the above as a true description of yaws, although he does so with some hesitation. We know that yaws is not a venereal disease and that it is not hereditary; still, it is more than probable that at the time Brickell wrote, slaves brought from Africa did bring framboesia into this country. Whether it continued to propagate itself in this country or not is another question. Undoubtedly from time to time cases of yaws are seen in this country among those who have come from endemic areas. Wood has collected in the article referred to all reported cases, both of extraneous and indigenous origin, seen in this country. The claim of McMurran made in 1900 that much of the so-called smallpox seen in Virginia was in reality yaws, we are inclined to dismiss as improbable. In 1858 McDowell, of Columbia, Texas, reported the case of a negro child with an ulcerating fungus growth about the anus, and states that its mother had yaws. In 1878 Jones, of New

Orleans, presented a case with the diagnosis of yaws, to his local society, but this individual was a native of the Isle of Bourbon, off the coast of Africa. In 1896 Matas, of New Orleans, reported yaws in a negro who had not been outside of the State of Louisiana. The diagnosis in this case was confirmed by Dyer. In 1909 Wood saw a case in Wilmington, N. C., which he believed to be yaws, and he is inclined to the opinion that much of the mild syphilis seen among the negroes in the South is, in fact, not syphilis, but yaws.

We must admit that a careful reading of Wood's valuable paper has not convinced us that yaws is, at present at least, indigenous in the United States. It would be well, however, for practitioners especially in the southern states, to bear this possibility in mind.

The Virus.—*Treponema pertenuis*, also known as *Spirocheta pertenuis*, *Spirocheta pertenuis*, and *Spirocheta pallida*, was discovered by Castellani, as we have already stated, in 1905. It is a slender spiral, varying in length from four or five to twenty microns. It requires prolonged contact with the stain in order to react, but good results may be obtained by the Giemsa or Leishman method. Since there are marked variations in length of this organism, there are similar differences in the number of the coils; also in their uniformity. As a rule, both extremities of the parasite are pointed, but one or both may be blunt and, more rarely, there is seen an individual which presents drum-stick forms. No undulating membrane has been found. The resemblance between this spirochete and that of syphilis is so close morphologically that differentiation by microscopic examination is uncertain. Now and then some investigators, studying these organisms comparatively, point out slight morphologic differences, but this simply means differences in the two species or strains which are under observation at the time. This spirochete is most easily and certainly found in the nonulcerative lesions. It is present, at least often, in the ulcerating tissue, but in this material it is accompanied by many other organisms. In framboesic patients this spirochete is found not only in the papules, but in the spleen and lymphatic glands. Extracts of framboesic material containing *T. pertenuis* inoculated into monkeys produce the disease, but when the organism has been removed from such extracts by filtration the preparation is rendered inert. Noguchi has grown cultures of this organism in sterile ascitic or hydrocele fluid to which a bit of fresh sterile kidney from the rabbit has been added.

Transmission.—So far as we know, this disease is transmitted from the infected to the uninfected only by contact and it is necessary that the recipient should have some break in the continuity of his cutaneous covering in order to receive the virus. Under this supposition, susceptibility to the disease consists in having some open avenue through

which the virus can enter the body. Naturally, the contact between the infected and the uninfected or between the donor and the recipient may be either direct or indirect. Direct contact may be by nursing, kissing, fondling, and sexual intercourse. In endemic regions mothers are frequently infected by their children, and occasionally children are infected by their mothers. It is said to be a well-known fact among negro tribes along the Congo that a mother having yaws should not sleep with her child and that if she does so she is likely to transmit the disease to it. Given an open specific sore on one individual and an open nonspecific sore on another, the specific agent may be transmitted from the former to the latter by direct contact, by clothing, by dressings, by insects, whether these be of biting or nonbiting varieties. Castellani examined the intestinal contents of a certain number of house flies and finding no evidence of the treponema in these, he permitted others of the same batch to feed upon a yaw sore and afterwards placed some of these on scarified spots over the eyebrows of several monkeys and kept them in this position by means of gauze for two hours. One of the monkeys became infected and developed the disease. Bahr is inclined to the opinion that the treponema is transmitted by biting insects, the species of which are probably not identical in the different endemic areas.

Control and Eradication.—That this disease may be completely eradicated from a community has been demonstrated in the results obtained by means of segregation of the infected. Thirty years ago, Rat, who had been largely instrumental in the eradication of this disease from certain of the Leeward Islands, wrote as follows:

“Can yaws be extirpated from any country by segregation? This, of course, can only be done if the disease is not hereditary. We may, I think assume that it is not hereditary. In that case the reply is, yes: yaws can be extirpated from a country by segregation, but by general segregation only. It is evident that the isolation of a few cases of a contagious disease, while 12 times as many, or more, are left at liberty, can never end in the eradication of that disease. And to be general, segregation must be compulsory. The community, therefore, which cannot afford the expense of compulsory, general segregation, is wasting money in attempting the impossible by adopting any less radical measure. But, though general segregation may, if persisted in for a considerable time, cause the disease to disappear, it by no means insures its nonrecurrence. For the disease may be disseminated again by its reappearance in those who had been segregated and who had been thought radically cured, or by importation from abroad. Something else, therefore, is wanting besides even general segregation to both eradicate and prevent the recurrence of the contagion. This something is an improvement in the sanitary surroundings of those among whom the disease originates and spreads, in the form of wholesome food and cleanliness, which can only be brought about by education and by remunerative industry. For such people education must be compulsory and free or assisted; and they must be provided with a market for the fruits of their labor. The disappearance of the disease has ever followed the improved social condition of the inhabitants of every country in which it has prevailed, even without either general or even partial segregation. That partial segregation is alto-

gether useless, I do not mean to assert, but what appears to me plain is that it cannot possibly effect what it is intended to achieve, viz., the extirpation of the disease, and that the expense connected with it is so enormously out of proportion to any result that it may produce, that it would be wiser to devote the considerable sums of money which have been spent in some colonies in the vain attempt to eradicate it, to improving the social condition of the people. The small colonies in which it is most prevalent cannot afford to provide shelter, food and attendance for all those who are affected with yaws during the long period required for the cure of the disease. All that can be done is to compel their attendance as out-patients on certain days at a public dispensary until they are declared cured by the medical officer, and to decide on a rational treatment of the affection which should be strictly carried out. The erroneous ideas which are entertained by some as to the proper treatment of the disease have been, unfortunately, the cause of its extensive persistence in some places from which it should have been long since entirely eradicated."

The discovery that arsphenamine acts so promptly and so thoroughly in the treatment of this disease encourages the idea that it may be eradicated with comparatively little effort from any community. Prolonged detention in a yaws hospital is no longer necessary. Practically all cases can be cured in a short time and this means that their ulcers heal and that as sources of infection they cease to exist.

Bibliography

- BREDA, A.: Report on Yaws, the New Sydenham Society, p. 259.
CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, London, 1919, Bailliere, Tindall & Cox.
CHARLOUIS, M.: Report on Yaws, the New Sydenham Society, p. 285.
MANSON-BAHR, P.: Tropical Diseases, London, 1921, Cassell & Co.
NICHOLLS, A.: Report on Yaws, the New Sydenham Society, 1897, clxi, 241.
NUTTALL, G. F. H.: Johns Hopkins Hospital Report, 1899, viii.
RAT, J. N.: Yaws: Its Nature and Treatment. Report of the Medical Officer of the Leeward Islands, 1891. (This report contains all the literature on this disease down to 1891, arranged chronologically.)
STRONG, R. N.: Phil. Jour. Sc., 1910.
WOOD, E. J.: Am. Jour. Trop. Dis. & Preventive Med., 1915, ii, 431.

CHAPTER XXVI

THE KALA-AZARS

I. GENERAL LEISHMANIASIS

Dumdum Fever; Cachectic Fever

Description.—This is a specific and chronic disease, characterized by an irregular fever, accompanied by enlargement of the spleen, and due to an organism known as *Leishmania donovani*. According to Ross, the name should be “kala-jwar,” signifying the black disease. The agent concerned in the transmission of this disease has not been determined with any certainty, although certain insects, especially those belonging to the genus *Clinocoridae*, are suspected. Further detail on this point will be given later. The dog is the only domestic animal, so far as is known, which suffers naturally from this disease, although it may be induced experimentally in other animals. In a disease so insidious in its development, early recognition is difficult. The fever of kala-azar is distinguished from that of malaria by the greater irregularity in the remission in the former disease. English physicians in India have given attention to these remissions, and Rogers reported some years ago that by taking the temperature every four hours he found two remissions each day. He believed this to be diagnostic of the disease. It is quite certain that there is a prefebrile stage which is not characterized by any marked symptoms and consequently, the period between infection and the onset of marked fever cannot be determined. It is, however, believed to range from three weeks to as many months. The febrile stage may develop slowly or it may be marked by a distinct rigor or chill, and this may occur daily. The febrile stage usually extends from three to six weeks, when the temperature falls and the subsequent progress of the disease is known as the apyrexial stage, although careful temperature measurements will in most cases show daily elevation generally not exceeding 100°. This afebrile stage is frequently terminated by the reappearance of chills and fever. Afebrile and febrile periods now alternate, while the spleen invariably, and the liver sometimes, enlarges. The flesh disappears from the chest and limbs, while the abdomen continues to enlarge, giving to the individual much the appearance so plainly in evidence among starving people. The anemia increases, while with equal step bodily weakness and mental depression mark the last stages of the disease. Scorbutic symptoms, such as hemorrhages from the gums, nose, bowels, and subcutaneously, may appear. There may be

cutaneous eruptions and even ulcerations, but these are not characteristic of this form of leishmaniasis. Diarrheal and dysenteric attacks may supervene and hasten the fatal ending. According to Castellani, the duration of the disease usually lies somewhere between seven months and two years and generally ends in death.

Laveran, who has recently (1917) published a most valuable and exhaustive monograph on "Leishmanioses," classes kala-azar as the visceral form of the disease caused by the leishmania, while he makes the Oriental sores cutaneous manifestations of leishmaniasis. This author states that kala-azar or visceral leishmaniasis shows the same clinical signs in its development in adults and in infants. In the adult, the initial progress of the disease is insidious and is accompanied only by sensations of weakness and slight febrile manifestations. Usually the physician is not consulted until the disease has developed markedly. At this time the two fundamental symptoms are an irregular remittent fever and a more or less marked hypertrophy of the spleen. Since both of these symptoms are constant in malarial fever, kala-azar and malaria were confounded for a long time. The fever of kala-azar is distinguished from that of malaria by its greater irregularity and by the fact that it is not affected by the administration of quinin. The hypertrophy of the spleen is quite as marked in kala-azar as it is in malaria. In the former disease there may be hypertrophy of the liver, but it is less marked than that of the spleen. As kala-azar advances, marasmus, with continued hypertrophy of the spleen and liver, gives to the patient a characteristic appearance. Anemia becomes more pronounced, nasal and gingival hemorrhages occur, and cutaneous eruptions are common. In many cases there is edema of the lower extremities; more rarely, ascites. As a rule, death is caused by secondary infection; dysentery, pneumonia, or noma.

In infants the two characteristic symptoms of kala-azar, irregular fever and splenomegaly, are not in evidence, but the disease proceeds with greater intensity and anemia develops more speedily and more markedly. The skin and mucous membranes are very pale. The face is blanched and presents a death-like appearance. Edema of the face and extremities is frequent. Hemorrhages and ulcerous gingivitis are common complications. In children death frequently occurs within three months, although the disease has been known to continue as long as three years, and recoveries are not unknown.

Kala-azar in dogs presents much the same symptoms as those observed in man. In this animal there is often in the later stages paralysis of the posterior extremities. The disease does not seem to be so fatal in dogs as in man, although death does occur in the dog and is accompanied by marked hypothermia. While the geographical distribution of human and canine kala-azar differs in localities to some extent, there is correspond-

ence when large areas are studied, and at present the disease in man and in dogs seems to be identical in etiology, symptomatology, and pathology.

A positive diagnosis of kala-azar cannot be made without the detection of the parasite. It has been found, even in early stages of the disease, in the peripheral blood. Castellani and Chalmers have the following to say concerning the diagnosis:

"The only certain method of diagnosis is to find the parasite, and as Donovan and Patton have reported its frequent occurrence, even in early stages, in the peripheral blood, this should be possible, especially if aided by dilution with normal saline solution, centrifugalization and examination of the leucocytes. In our experience, the search for the parasite in the leucocytes of the peripheral blood requires an extremely long time, and is often negative. If the parasites cannot be found in the blood, an attempt may be made to find them by the examination of the exudate obtained by exciting artificial pustulation of the skin by some irritant, as suggested by Major Cummins. Failing this, there is puncture of the spleen or of the liver, and withdrawal of the blood, which can be examined by the microscope. The diagnostic puncture of the spleen in the tropics, is, however, not to be undertaken lightly, because splenic enlargement due to leukemia is by no means unknown, and puncture of the spleen in this disease, or, indeed, in that of chronic malaria, may lead to most unfortunate results. The blood of the peripheral circulation should therefore be examined to exclude leukemia.

"Certainly, the first thing to do is to examine the peripheral blood and exclude leukemia. Secondly, the coagulability of the blood should be tested by Wright's method, and if found to be decreased, the puncture should not be performed. Thirdly, if the puncture is to be carried out, the liver should be chosen for exploration, not the spleen, particularly in the later stages, in which hemorrhages are to be feared. In the early stages there may not be so much risk, but it must be done with the greatest care, aseptically, and the patient must be kept at rest for some time afterwards, the site of the puncture being covered with an aseptic pad and a firm bandage. The syringe should be sterile, and perfectly dry. Rogers recommends that a dose of 30 grains of calcium chlorid in a couple of ounces of water be administered directly after a puncture, in order to promote coagulability of the blood.

"In the early stages the diagnosis has to be principally made from acute malaria and typhoid, when the positive signs in favor of kala-azar are: (1) Presence of the characteristic daily double remission of the fever; (2) absence of constitutional symptoms, proportional to the severity of the fever; (3) absence of malarial parasites and Widal's reaction, though, of course, the latter reaction is negative in true typhoid during the first week; (4) marked enlargement of the spleen; (5) great leukopenia, especially in relation to the erythrocytes, which, however, may also be found in typhoid and malaria; (6) increase in mononuclear leucocytes; (7) presence of *Leishmania donovani* in the leucocytes.

"In advanced cases the diagnosis has to be made from malarial cachexia and ankylostomiasis by (1) the presence of *Leishmania donovani* in the leucocytes of the peripheral blood, or in the juice from the liver and spleen; (2) by the absence of the typical febrile attacks of subtertian or tertian fever; (3) by the absence during the febrile attack of malarial parasites; (4) by the absence of ankylostomes, or if they are present, by continuation of the symptoms after their expulsion. Mixed infection of kala-azar and malaria may occur."

History.—When the English took possession (1869) of the territory lying to the east of the Brahmapoutra River known as the Garo Hills, they

found prevalent among the natives of this region a disease known in the vernacular as kala-azar, and which was believed at that time by British medical officers to be a severe form of malarial cachexia. In succeeding years this disease either actually spread, or further penetration of the country by the British showed its wider distribution. By 1875 it had apparently become an epidemic, causing a high death rate. The first publication on the disease was made by Clarke in 1882 on notes of 120 cases observed by McNaughton, the civil medical officer of the District. By 1889 this disease in epidemic form was found in Assam, where an investigation by Giles led to the conclusion that it was due to hookworm infection. There can be no doubt that ankylostomiasis was then prevalent, as it is now, in that part of India, and the mistake of attributing kala-azar to this infection is excusable. In 1894 Stephens, after quite a thorough study, came to the conclusion that, while kala-azar is not malaria, it is closely related to this disease. In 1897 Rogers and 1899 Ross, both experts in malarial diseases, reached the conclusion that kala-azar is a form of malaria. In 1902 Bentley, depending upon serum reactions, came to the conclusion that the causal agent is the *Micrococcus melitensis*; in other words, this authority believed kala-azar to be a form of Malta fever.

In 1900 Leishman had under his charge in a military hospital at Netley, England, a sick soldier who had been invalided home from India. This man had been stationed at Dumdum, a most insalubrious post about seven miles from Calcutta. This was the only post at which this man had been stationed in the Orient and it was quite certain that, whatever the nature of the disease from which he suffered, it was acquired at this post. This man was admitted to the Netley Hospital in April, 1900, and was under Leishman's observation for seven months, when he died. The diagnosis under which he was admitted to the hospital was "dumdum fever" complicated with dysentery. The man was greatly emaciated and ordinarily his temperature was below normal, but from time to time he showed an irregular fever. Frequent examination of the blood failed to show any form of malarial parasite. At autopsy the spleen was found to be greatly enlarged, while the only other notable lesions were cicatrices from intestinal ulcerations. In smears from the spleen Leishman found a large number of organisms which he was unable to identify with anything he had previously seen. These bodies were round or oval with a diameter of from two to three microns. When stained by the Romanowsky method they showed two chromatin masses, a large and a small one, the former round and staining slightly, while the latter was rod shaped and stained deeply. The latter showed a linear structure corresponding to the rhizoplasts of Novy and Mesnil. Leishman observed accumulations of from 20 to 50 of these organisms in certain cells. At that time Leishman was

studying nagana, and from comparisons between the organisms found in the spleen of the dead soldier and those obtained from the viscera of a nagana rat he was inclined to the opinion that the new organism belonged to the trypanosomes.

Leishman did not publish these observations until May, 1903. In the following July, Donovan, serving at the Military Hospital at Madras, reported that he had discovered, both at autopsies and by puncture of the spleen during life in patients suffering from an irregular fever, organisms similar to, if not identical with, those described by Leishman. Donovan sent stains of these organisms to Laveran and Mesnil for identification. The French experts were unable to identify these bodies with any hitherto known organisms. They concluded that they could not be classified with either plasmodia or trypanosomes, and proposed to give to these newly discovered bodies the name *Piroplasma donovani*. It should be stated that up to that time Donovan had found this parasite in ten cases of irregular fever. The identity of the organism discovered by Leishman and Donovan was soon established and Ross, believing it to belong to a new species, proposed to give it the name *Leishmania donovani*. This designation has continued up to the present time without any one being able to determine its exact place in the classification of pathogenic organisms. Within a few months Donovan was able to add from his own service 16 cases in which he had demonstrated the presence of this organism during life by puncture of the spleen or liver. All of these cases were marked by irregular fever, pulmonary congestion, occasional subcutaneous hemorrhages and buccal ulcerations, with increase in the size of the spleen. Treatment with quinin, arsenic and salicylate of soda was without effect.

Following these basic discoveries, confirmatory and amplifying reports began to come in. In 1904 Rogers drew blood from the spleen in a case of kala-azar into sterile sodium citrate solution and incubated at 22° C. Under these conditions parasites developed into flagellates. This demonstration of the flagellated stage was of some negative value in attempts to properly locate the organism, but these flagellates were found to be without an undulating membrane. Laveran concludes from this that *L. donovani* does not belong to either the *piroplasma* or the *trypanosoma*.

Christophers made important contributions to our knowledge of the anatomic and histologic changes induced in the tissues of the body by this parasite. It appears that when introduced into the body it at first takes up its residence in the endothelial cells, in the capillaries of the spleen, bone-marrow, lymphatic glands, intestinal mucosa, and in some instances in the larger blood vessels. In the endothelial cells it multiplies simply by fission until a single cell may contain, according to Leishman, more than 200. When the endothelial cells rupture, their guests are discharged into the blood where, in part at least, they are taken up by the white blood

corpuseles, in all varieties of which the organism may be found, although they seem to be most abundant in the polymorphonuclear leucocytes. In some cases they are so abundant in the leucocytes that they can be detected by the examination of the peripheral blood. In such cases a blood smear from the finger, properly stained, demonstrates the parasite. It is not believed, or at least not demonstrated, that the flagellated form develops in the human body. As has been stated, this form does appear when citrated blood from the spleen of a case of kala-azar is incubated at a low temperature. According to Patton and others, there are certain bugs, among which is the bedbug, in which this parasite develops into flagellated forms. It is not known, however, that an insect host is essential to the life-cycle of this organism. The relation of insects in the distribution of this virus will be discussed later.

A most important extension of our knowledge of kala-azar was made by French physicians in northern Africa. In 1904 Cathoire at La Goulette, Tunis, saw a child seven months of age who was dying after having manifested the symptoms of kala-azar. Autopsy revealed a greatly enlarged liver, in the pulp of which *L. donovani* was demonstrated. The African organism was for a while, and is still by some, believed to be sufficiently different from *L. donovani* to deserve a special name, and Nicolle designated it as *L. infantum*. It is still a matter of discussion as to the duality of kala-azar as seen most typically in India, and the infantile kala-azar as seen most typically in the Mediterranean basin. Laveran, who speaks with authority upon this subject, thinks that there are no essential differences in the parasite as found in adults and in children, and, following this author, we recognize no difference between *L. donovani* and *L. infantum*.

The discovery by Cathoire interested both laboratory workers and practitioners in all countries roundabout the Mediterranean and caused them to look for this disease within their own provinces. Nicolle showed that *L. donovani*, or, as he called it, *L. infantum*, was easily susceptible to cultivation in the Novy-McNeal medium even when this was simplified by the omission of meat and pepton. This discovery has greatly facilitated the study of these organisms. Nicolle and his colleagues furthermore demonstrated that the common monkeys of northern Africa (*Macacus*) are easily inoculable with the kala-azar parasite, that the native dogs of Tunis have kala-azar naturally, and that infantile and canine kala-azar are quite certainly identical. Nicolle and Comte found that in the spring 1.8 per cent of the dogs of Tunis bear this infection. The Sergeants (Ed. and Et.) found in Algiers this number to be as high as 7.2 per cent, and in a village near Messina, Basile found, out of 33 dogs examined, 27 infected. He reports that infected dogs were found in every house in which human kala-azar had been reported. Furthermore, he discovered that in some houses in which infected dogs were found and in which there had been

up to that time no cases of human kala-azar, individuals subsequently were attacked by this disease. Canine kala-azar has been found in Italy as far north as Rome, in Greece and neighboring islands, in Asia Minor, and along other portions of the Mediterranean zone. In 1905 Pianese demonstrated that an irregular fever which had been prevalent in Naples for many years is, in part at least, infantile kala-azar.

Geographical Distribution.—The distribution of kala-azar, as at present known, is of great interest to the epidemiologist, inasmuch as it presents peculiar, conflicting, and, in some cases, apparently contradictory problems. The epidemiology of this disease in India has been the subject of frequent study and the classical paper on this subject by Rogers in his work on "Fevers in the Tropics" (1910) should be read by every epidemiologist whether he is interested especially in kala-azar or not. At present this disease is well known and frequently observed from the Delta of the Ganges, up that river to Dinapur, and endemic areas are found on both sides of the Brahmapoutra up to the foothills of the Himalayas. Outside of these areas, which are contiguous, the only other endemic area at present known in India, is at Madras. The entire northwestern region appears to be free from this form of leishmaniasis, while the cutaneous form of this infection is known and has been long prevalent on the Upper Ganges in and north of Delhi; indeed, "Delhi boil" is one of the ancient names for cutaneous leishmaniasis. It is also known around the Gulf of Cambay and on both sides of the Indus River. Neither form of leishmaniasis is indigenous, so far as is known, in Bombay or in any of the country along that coast. It is a striking fact, observed not only in India, but in some other regions, that internal and cutaneous leishmaniasis are not found in the same region.

In 1854, according to Rogers, an epidemic, first manifesting itself in the swampy district of Jessore to the east of Calcutta, traveled along the roads most frequently used and continued its progress until 1873, during which time it greatly reduced the population and in some districts so interfered with agriculture that these parts were left barren. During its progress in 1868 it reached the town of Burdwan, in which it raged with such malignity that it became known as "Burdwan fever." Rogers, who made a study of the records pertaining to this epidemic, writes of it as follows:

"Not only did the disease extend along the lines of communication, just as I have mentioned was always the case with the later Assam epidemic, but, like the latter, its progress was also obstructed by lack of ready intercourse between one place and another, as shown by the entire escape of an area surrounded by rivers and small shallow lakes, and thus cut off very much from the surrounding country. Further, the fever took from 1862 to 1869 to travel round from the northern part of the area first attacked to the west of the Bhagarathi River to a place only a few miles to the northwest of it on the same stream, but with no direct communication between the two, thus bearing out Dr.

Jackson's statement, "Wherever there has been active intercourse, the fever has traveled; where there has been little or none, it has died out."

"The next point of interest is the cessation of the epidemic, for this took place as soon as it reached the borders of the alluvial soil over which it had been extending, and arrived at the borders of the much drier laterite formation and the rising ground at the foot of the Chota Nagpur plateau, and the low hills of the Sonthal Pergunnahs. This was very marked in the Midnapore district where the alluvial parts were severely overrun, but the fever never seemed to be able to get a firm footing on the laterite areas. This cessation of the spread is precisely parallel to the influence of the hills surrounding the Assam Valley in restraining that of kala-azar, for it was only the lower ranges of the Garo Hills with their alluvial valleys and basins which were severely affected by the Assam outbreak.

"The terrible nature of the Burdwan epidemic depended largely on the affected areas being much more densely populated than the later attacked parts of Assam, for no less than a quarter of a million persons are estimated to have died in the Burdwan division alone of the epidemic fever. The exact nature of the disease gave rise to almost as much controversy as its Assam prototype, the question of its contagiousness being specially warmly debated. As it was almost universally regarded as being unquestionably malarial in its nature this very fact was held by some to be positive proof that it could not be infectious; just as was later on argued in Assam. Dr. Jackson concluded his very able report by writing: 'While I believe the fever to be malarial in its origin, and to have some malarial characteristics, I believe it to be not a simple, but a contagious malarial fever; that is probably typhomalarial, and that it has not been produced in Burdwan itself but imported.' In the descriptions of the disease its identity with kala-azar is quite clear, with the exception that a few cases terminating rapidly with coma were recorded—doubtless cerebral malaria, naturally regarded as part of the outbreak. It is also worthy of note that whereas the Burdwan division before this epidemic was looked upon by the native inhabitants as a sanitarium, it has ever since retained a name for feverishness, and I have recently found the parasites of kala-azar in several typical cases of the sporadic form of the disease from the Burdwan district, so that the epidemic has left behind it the sporadic affection, just as kala-azar has done in the parts of Assam it has devastated."

Whether the Assam epidemic (1875-1898) was a continuation of that which had afflicted Lower Bengal and which was known as Burdwan fever, or was introduced into Assam from some other source, has not been and probably never can be definitely determined. The Assam epidemic first attracted attention in the lower province of that country known as Garo Hills and gradually spread up the Brahmapoutra River, following apparently the construction and use of the trunk road, and finally dying out in Nowgong, a northern province of Assam. In the last-mentioned province, according to Rogers,

"the fever death rate rose by leaps and bounds from an average of about 4,000 a year previously to 1892 up to over 14,000 in 1897, and then declining still more rapidly to under 6,000 in 1900, and an average of about 4,000 once more during the last five years."

Concerning the epidemic in Nowgong, Rogers writes:

"During this decade (1891-1901) Nowgong felt the full force of the epidemic, and its truly appalling nature is revealed by the fact that in these ten years, instead of an

increase of ten per cent, as between 1881 and 1891, there was actually a decrease of twenty-four per cent of the total population of the district; or, if the indigenous Assamese are alone considered, the loss was no less than 31.5 per cent, or almost one-third of the people—a death rate which far exceeds that of recent plague, and for which it would be difficult to find a modern parallel, unless it be that of the closely-allied sleeping sickness of Africa.”

Writing of the Assam epidemic, Manson says:

“The epidemic advanced slowly along the valley of the Brahmapoutra, taking seven years to spread less than 100 miles. The introduction of the infection into a village was almost invariably traced to some one coming with the disease on him from an infected locality, though some isolated localities escaped in a remarkable manner. Generally it clung to a place for about six years, and then disappeared without any apparent change in the local conditions. A house seemed to retain the infection for many months; the natives considered that it could not be reoccupied with safety under one year. During the course of the epidemic, kala-azar never extended far above the level of the Brahmapoutra valley, the disease appearing first at the foot of the hills, and then spreading between them along the patches of low, flat, terai country. On account of its deadliness, kala-azar as it swept onwards became a terror to the natives. Those suffering from the disease were turned out of the village; sometimes they were made unconscious with drink, taken into the jungle, and burned to death. Some villages cut off all communication with neighboring villages for fear of infection; other villagers deserted their homes and even migrated to a different district.”

There has been no epidemic of kala-azar in or about Madras and the sporadic cases observed in that city have come largely from certain quarters which are noted for their insanitary conditions and their crowded dirty population. During seven years (1903-1909) Donovan saw 530 cases of kala-azar in the General Hospital at Madras. In closing our remarks on the distribution of kala-azar in India, we wish to emphasize the fact that internal or splenic and cutaneous leishmaniasis are not found in the same neighborhoods in this country. This is a strong argument in favor of those who, notwithstanding the apparent identity of the virus, believe that these are two distinct specific diseases. Another most important observation is that natural leishmaniasis in dogs has not been found in that part of India where kala-azar is endemic. Moreover, native dogs in these regions are highly resistant to inoculation with *L. donovani*. While, as we have stated, 8.8 per cent of the dogs in Algiers in the spring and summer were found to bear the leishman infection, Donovan examined 1,150 dogs in Madras and failed to find one infected.

Castellani has reported one case of kala-azar observed by him in Ceylon, but this patient was a Singhalese and there is no telling where he contracted the infection. If kala-azar exists in Ceylon it is very rare and has escaped observation. In an incidental way, Castellani says that he found a few dogs at Colombo in 1911 bearing the leishman infection, but he does not stress this point and adds that since Colombo is one of the

great harbors of the world and is visited by ships from all parts, the infected dogs may not have been native to the Island.

There seems to be quite an extensive endemic area in China, the southern border of which is the Yang-tse-Kiang River; the eastern, the shores of the Yellow Sea; the northern, the great wall, while the western lies along a line drawn some distance west of Peking, slightly west of Chang-Te and Hou-Peh, and extending down to the Yang-tse-Kiang. In 1904 Marchand and Ledingham demonstrated internal leishmaniasis in a German soldier at Leipzig. This man had served in China, had visited no other part of the Orient, and it is assumed that he acquired the infection in China. Since that time Kerr, Aspland, Bassett-Smith, Hill, and others have reported sporadic cases of visceral leishmaniasis in the area already indicated. Hill reports having seen 11 cases of infantile kala-azar in Peking within two years and Jérusalem states that infantile kala-azar is endemic in certain parts of Shantung. It is more than probable that further investigation will show a wider distribution of this disease in southern and western China.

Yakimoff and other Russian physicians have shown that kala-azar in both adults and children is by no means uncommon in Turkestan. The disease has been observed in the cities of Tashkent, Samarcand, Boukhara, as well as in smaller villages throughout Turkestan. Petroff saw a case in Petrograd, but this patient came from Turkestan. Gurko, during a short visit to Tiflis, discovered nine cases, and the disease is said to be endemic in Transcaucasia.

Passing from Asia into northern Africa, we find that the distribution of leishmaniasis has been studied quite thoroughly by French physicians. Here, as in India, the internal or splenic form of the disease, is, geographically, quite apart from the cutaneous form. The former is frequent in and about the City of Tunis where many cases of infantile leishmaniasis have been found. In the same region, as we have already indicated, canine leishmaniasis is common and there are good reasons for believing that children become infected from close association with infected dogs. Cutaneous leishmaniasis has so far been observed only in southern Tunis and at one location, Gafsa.

Infantile leishmaniasis has been found in Algiers and Tripoli, in both of which countries canine infection has been found in some sections at least and during certain seasons of the year, to involve 8.8 per cent of these domestic animals. In Egypt kala-azar is not indigenous, or, if so, it is very rare; but in the British Sudan it seems to be unusually common. As early as 1904, *L. donovani* was detected in the spleen of a child in the hospital at Omdurman, and since that time cases have been reported along the Blue Nile and in that part of the Sudan nearest Abyssinia. Archibald, who has studied the disease in this region, has been able to infect monkeys

by feeding, from which the conclusion is drawn that the Sudan variety at least, may be due to infected drinking water. Infantile leishmaniasis has been found in certain Mediterranean Islands and in all European countries bordering on this Sea. In Sicily it has been found in coastal villages all around the Island and it is signally present in Palermo and Messina. Numerous cases have been detected in Calabria and scattered ones up the coast to Naples where, according to Pianese, the infantile form has long been known under the name of infantile anemia. Sporadic cases have been observed along the coast from Naples to Rome. Contrary to the condition existing in India and in Tunis, cutaneous leishmaniasis in Italy may be found in the same neighborhood with the splenic form. It is said that in Sicily and Calabria both the cutaneous and internal manifestations of leishmaniasis may occur in the same place and at the same time.

Wenyon reports both infantile and canine kala-azar as occurring on the Island of Malta. According to Bassett-Smith, Weld, and Ward, the disease has been detected in British soldiers and sailors at Malta.

Cases of the infantile form of this disease, as well as of the canine form, have been reported along the Mediterranean Coast of Spain and farther inward in the provinces of Malaga and Granada. An occasional case has been observed in Portugal, and out of 300 dogs examined at Lisbon eight were found to carry the leishman infection.

Within recent years Greek physicians have called attention to the probable existence of this disease in their country and especially on the Islands of Hydra and Spetzia in the Greek Archipelago, for a long time; indeed, some think they have found passages in the writings of Hippocrates which refer to kala-azar. It seems that in 1835 Roeser wrote concerning a disease on the above-mentioned islands which still continues in these localities and which since the discovery of the parasite has been shown to be leishmaniasis. However this may be, it is quite certain that both infantile and canine kala-azar may be found in sporadic form throughout Greece and on several of the islands of the Greek Archipelago.

Up to the present time the existence of visceral leishmaniasis or true kala-azar in the Western Hemisphere has not been demonstrated. It is true that in 1897 a case was reported at Asuncion in Paraguay, but the patient was an Italian, forty-seven years of age, and where he became infected is not known. There is an American leishmaniasis which affects the skin and mucous membrane and which will be discussed later.

Seasonal Relations.—It will be seen from its geographical distribution that kala-azar is endemic only in tropical and subtropical countries. From the fact that he did not get growths in his blood cultures until he lowered the temperature to 22° C., Rogers believes that the flagellated form of this virus or its extracorporeal development can occur only when the temperature of the air is not above 75° F. This fits in with the theory that a

period of the life-cycle of this virus occurs in some insect. On this point, Rogers writes:

“Taking everything into consideration, I think there is sufficient evidence to prove that the great majority of patients become infected in the cold season, and I am inclined to think that infection will ultimately be found to be limited to this time of the year. The importance of this fact in connection with prophylactic measures is clear, as it will greatly simplify matters if precautions against infection have only to be taken during a few months of the year.”

According to James, kala-azar is ordinarily confined to low, humid places along water courses and where rain is frequent and abundant. According to Lignos, on the Island of Hydra, kala-azar reaches its greatest intensity in winter and completely disappears in summer. It may be said that on this Island the average temperature from November to April runs from 18° to 22° C. and it is during this time that the greatest number of cases develop. Basile takes the winter temperature of Hydra, Sicily, and other Mediterranean Islands in which kala-azar is known, as an indication that the parasite requires an intermediate cold-blooded host in the cycle of its development.

Susceptibility.—In India, all ages and both sexes are susceptible, but, quite naturally, the greater number of cases appear in children. In the Mediterranean region children, and especially young children, are so greatly in excess among those infected that, as we have seen, the disease is known as infantile kala-azar. In the endemic areas, Caucasian visitors, although not wholly exempt, rarely become infected. This, however, is dependent upon the intimacy with which they come into contact with the natives. Price says that he knows of no instance in which a European who cohabited with an infected native woman escaped kala-azar. This does not mean that the disease is venereal, but it suggests the transmission of the parasite by some insect which clings rather closely to the body, such as a bedbug, louse, or flea.

From a study of the epidemiology of this disease, we conclude that close contact, such as exists between members of the same family or those occupying the same house, is essential in its distribution. On this point, Rogers says:

“Several of the cases already referred to illustrate very well the extraordinary tendency of this disease to attack a number of persons in the same family or household, but the frequency with which this is the case will be better realized from the following figures relating to 20 successive Assamese patients seen in the Nowgong Hospital. Among their near relatives no less than 123 persons had been attacked by kala-azar, only two of whom recovered while but 44 of their near relatives had escaped the infection; or to put it another way, no less than four-fifths of these patients had lost half or more than half of their relatives within three to five years, so that it is easy to understand how whole families have been destroyed, and so much land has fallen out of cultivation.”

Transmission.—A strong impression has been made upon students of this disease that it is transmitted by means of some biting insect. In India the bedbug, *Clinocorosis rotundatus*, has been suspected, and Patton has shown that when these insects are fed on cells containing the virus the parasite in the insect develops into flagellated forms. This development is not influenced by the temperature of the air. However, flagellated forms of similar parasites are found in this bug and the evidence that it is concerned in the transmission of kala-azar still remains incomplete. We have already called attention to the close coincidence between infantile and canine kala-azar in the Mediterranean area, and some strong experimental evidence justifies the suggestion that the parasite is transferred from dogs to children by the fleas which infest the former. In endemic areas in India, dogs exhibit a high degree of immunity to this infection and succumb to experimental inoculation only when massive doses are given. We have already called attention to Archibald's theory that in the Sudan infection takes place through the alimentary canal and is due to contaminated drinking water. In the course of the disease there are frequently intestinal ulcerations and it is altogether probable that the feces from such cases carry the virus. In India the progress of epidemics of this disease does not support the theory that the infection is water borne. It is possible that the disease may be transmitted by more than one agency. However, the problem of its transmission in the different endemic areas must be solved before the eradication of the disease can be accomplished. Manson, who speaks with authority, makes the following statement:

“Under natural conditions kala-azar, like other diseases caused by similar protozoal organism, is probably transmitted by a living agent. There are certain facts, however, which tend to suggest that the carrier need not necessarily be a blood-sucking animal. In the first place, the parasite in man is not, as a rule, in great abundance in the peripheral circulation. Secondly, the parasite is often present in ulcerations of the skin and of the intestinal mucosa, suggesting elimination by these organs. Mackie has found leishman-like bodies in the mucus of dysenteric cases of kala-azar. Thirdly, we know that although some species of *Herpetomonas* are fostered by blood-sucking flies, such as *Tabanus* and *Hematopota*, others are found in nonbiting forms, such as *Musca*, *Sarcophaga*, *Pollenia*, and *Fucellia*, which could become infected only by settling on ulcerations or on fecal matter. It is conceivable that such insects might transmit the infection of kala-azar by depositing the parasites on wounds and abraded surfaces. It has been suggested that there is a reservoir for leishmania in some of the lower animals, e. g., the house lizard. The history of the Assam epidemic is against this view, for it has been definitely shown that the disease was introduced and spread by man, and that it did not pre-exist in the invaded districts, as would have been the case had there been an animal reservoir.”

Eradication.—In the Assam epidemic Rogers proceeded in his prophylactic measures on the assumption of house infection. He moved infected villages and found that when the new village was located only 400

yards from the old one, infection in the former did not appear, while in the latter it sometimes continued for years. Quite obviously, there are defects in this method of dealing with a disease. No sharp line between the infected and the uninfected can be drawn and it must necessarily happen that infected persons along with the uninfected will be transferred to the new village carrying with them the infection. It was easy enough to do as Rogers did and to see that freshly imported coolies on the tea plantations of Assam did not get into the old infected villages but were located in newly-built huts apart from the natives and intercommunication denied, On this point, Rogers says:

"I have already mentioned the partial success of moving infected villages to new sites but a short distance away, which, taken with the strong evidence I collected in 1897 as to the infection being a house one, appeared to me to afford the most promising basis for preventive measures. Finding also that over a year before I went to Assam Dr. Dodds Price, suspecting the disease to be infectious, had placed 150 out of 200 freshly imported coolies in newly-built lines of houses, while the remaining 50 had to be accommodated in infected lines for want of room, I got him to work out the result of this measure. It was thus ascertained that although none of the 150 in the new lines had suffered from kala-azar during two years they had been on this badly infected tea garden, yet no less than eight, or sixteen per cent, of those placed in the old lines were already dead of the disease, and that, too, in spite of the fact that the new lines were but 300 yards from the old ones, a distance insufficient to prevent the spread of malaria through the agency of mosquitoes."

After a most careful reading of the excellent report by Rogers, we are convinced that his measures did protect immigrants into the infected region, but we are not so sure that his work was highly efficacious in even limiting the disease among the natives. We have the impression that among the latter the epidemic raged until it burned itself out.

There are certain obvious things to be done in attempts to limit and finally to exterminate this disease. In the first place, thorough sanitation, with hygienic housing, the destruction of house insects, the killing of infected dogs, the prevention of intimate contact between all dogs and children, the elevation of the plane of living of the common people, provision for their personal cleanliness, the prevention of overcrowding, the installation of uncontaminated water-supplies and of continued sewage disposal; when these things are done and their benefits secured for the masses of the people in endemic areas, the boundaries of these regions will gradually contract and ultimately disappear.

Bibliography

- BENTLEY, A.: *Indian Med. Gaz.*, 1904, p. 81.
 CASTELLANI, A., AND CHALMERS, A. J.: *Manual of Tropical Medicine*, New York, 1913, William Wood & Company.
 CHRISTOPHERS, S. R.: *Scientific Memoirs of Officers of the Medical & Sanitary Dept. of the Gov. of India*, 1904, 1905.
 DONOVAN, C.: *Brit. Med. Jour.*, 1903, ii, 79.

- LAVERAN, A.: *Leishmanioses: Kala-Azar, Bouton d'Orient, Leishmaniose Americaine*, Paris, 1907, Masson et Cie.
- LEISHMAN, W. B.: *Brit. Med. Jour.*, 1903, i & ii.
- MANSON, P. H.: *Tropical Diseases*, London, 1921, Cassell & Company.
- NICOLLE, C.: *Arch. de l'Institut. Pasteur de Tunis*, 1908, 1909, 1910, 1911.
- ROGERS, L.: *Fevers in the Tropics*, London, 1910, Hodder & Stoughton.
- ROSS, R.: *Report on the Nature of Kala-Azar*, Calcutta, 1899.

II. CUTANEOUS LEISHMANIASIS

Leishmaniasis tropica; Oriental sore; Aleppo boil; Delhi boil; etc.

Description.—There occurs in certain localities in tropical and sub-tropical countries frequent infection with a virus which causes the development of persistent single or multiple boils or sores. Many localities have acquired unenviable reputations on account of the prevalence of this affection among the inhabitants. This fact has given rise to a variety of names, such as Delhi, Aleppo, Bagdad, Oriental boil. There may be only one sore, but since the disease is auto-inoculable the number that may follow scratching with infected nails is unlimited. The sore is slow in development, persistent in its maturity, and tardy in its disappearance. In some endemic localities it is known as “yearly boil,” indicating that its victim may expect to bear his infliction for 12 months or longer. Usually the sores are located on the uncovered parts of the body, such as the arms, head, face, ears, feet, and legs. In experimental inoculation, from a few days to six or seven months elapse before there is any sign of local reaction. On this point Manson writes:

“The incubation period of Oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable Oriental sore which did not appear until five months after the patient had been exposed to any possibility of infection. Wenyon inoculated himself with Oriental sore in Aleppo; it was not until six and a half months later that a leishman-containing papule, subsequently developing into a sore, appeared at the site of inoculation. In other cases the incubation period has been as much as fifteen months, or even longer.

“There is very little reliable information about the presence or absence of constitutional symptoms. It is customary to describe the disease as nonfebrile. This may be true in most cases, but it is not invariably so. It is obvious that in a disease with, at least in some instances, a very prolonged incubation period, slight or even severe fever might be overlooked or misinterpreted. Oriental sore produces an immunity against itself. There must, therefore, be profound constitutional change. In other diseases attended with similar change, fever is almost invariably present at one time or another in their course. In the case just alluded to as occurring in Manson’s experience, a severe anomalous fever, of five or six weeks’ duration, preceded by eight months the appearance of the local lesions. In Wenyon’s case the development of the initial

papule was preceded by smart fever supposed at the time to be influenzal. Seeing, as has been pointed out, close connection of Oriental sore with kala-azar, this question of the constitutional symptoms in the milder disease is an important one, and should be carefully studied."

The initial appearance is in the form of a small papule, hard to the touch, and made up of infiltrated cutaneous tissue. Later the surface is scaly, dry, and white. This covering becomes moister, thicker, browner, and when removed or when it drops off, there remains a shallow ulcer. This discharges a purulent material and continues to grow larger by undermining and destroying the dermis. When fully developed the ulcers are generally about an inch in diameter, although larger ones may appear. The depth of the ulcer is quite variable. It is not accompanied by much pain. The tendency is to slow granulation and healing, which, as has been stated, usually requires several months. Death may occur from complications and more serious infections, but uncomplicated cutaneous leishmaniasis is not a fatal disease. The parasites may be found by smears made from the ulcer and stained by the Romanowsky method or some modification of this method, such as that of Leishman or Giemsa. According to Castellani and Chalmers, there are the following varieties of Oriental sore: (1) Oriental sore as it usually occurs in Asia, Africa, and south Europe, consists of one or more nodules, which slowly ulcerate and gradually heal by granulation; (2) the warty or verrucose variety, which has been observed by Ferguson, Richards and Archibald in the Sudan; (3) the keloid form, in which the nodules are pinkish, hard, and do not ulcerate; (4) the framboesic form, fairly common in the West Indies, where it is known as forest yaws; (5) the papillomatous variety, most frequently seen in South America, especially along the Amazon, where it is said to afflict not only man, but horses, mules, and donkeys.

In 1756 Russell, after having practiced medicine in Aleppo for 13 years, wrote an interesting book, entitled, "The Natural History of Aleppo and Parts Adjacent," in which he describes the sore which has given to this city an unenviable reputation:

"The natives reckon but two species of this disorder, and distinguish them by the names of male and female; but there is a third kind of cutaneous distemper, which, though it is commonly ascribed to the bite or sting of a common millipedes, or wood-louse, seems to me to be altogether of the same nature, though milder in degree."

"What they call the male distemper, makes its appearance in the form of a small, red, hard tubercle or pimple, which commonly passes some weeks unregarded, as it gives no manner of uneasiness; afterwards it begins to encrease, and usually comes to the size of an *English* sixpence, which, after some months, begins to be scurfy on the top; by degrees the little matter that oozes out of it, forms into a thick crusty scab; which, unless it is picked off, or otherwise disturbed, remains upon it till the parts underneath being healed, it falls off, and leaves but a very small mark. The whole of its duration is seldom above eight months.

"What is called the female species begins like the former; but after a month or

two it becomes somewhat painful, encreases often to double the extent of the male, discharges a good deal of the ichorous matter from under the scab, and by degrees comes to have the appearance of an indigested scorbutic ulcer, with a livid circle round it; but seems to be no deeper than the *tunica cellulosa*. In this condition it remains for several months, and is in general about a year from its first appearance before it is cured; but this is not a thing certain, many getting well some months sooner, while others remain several months longer. After it is cicatrized, it leaves an ugly scar, which remains thro' life, and for many months has a livid color. When they are not irritated, they seldom give much pain.

"The third kind of *Mal*, which they call the pinch of a millipedes, begins like the two others, but seldom grows larger than about twice the size of a large pin's head, and never changes its appearance, remaining a small tubercle for many months, without any pain, after which it usually throws off a few scurfy scales and disappears; but some remain a much longer time.

"It affects the natives when they are children, and generally appears in the face, though they also have some on their extremities; for most of them have two, three, or sometimes more, it being rare that they have but one. In strangers, it commonly appears some months after their arrival; and they have them not so frequently on the face as the natives; very few escape having them, but they seldom affect the same person above once; dogs and cats are as subject to the disease as men; it commonly breaks out upon the nose of these creatures."

History.—The first information concerning this disease furnished to the modern world is found in the book by Russell to which we have just referred. This was followed by similar reports by Hasselquist (1758), Hollande (1778), and Volney (1787). In 1829 Alibert, in 1833 Guilhou, and in 1854 Willemin, added to our knowledge of Aleppo boil.

In 1844 a French expedition against certain tribes in southern Algeria reached the Oasis of Biskra. In the camp at this oasis were 450 chasseurs of the Third African Battalion. At first, these men were more or less affected with diarrheas, malarial fevers, and ophthalmias, but at the oncoming of winter, all, with the exception of the officers, developed cutaneous sores. Seventy-five of these were sent in January, 1845, to the hospital at Constantine, and later Biskra was wholly abandoned. The nature of the disease manifesting these cutaneous lesions was wholly unknown and it was believed that the men had been stricken with leprosy. Later it was shown that Biskra boil or sore was identical with that which had long been known at Aleppo. Various theories were advanced to account for the specific insalubrity of the location. It was suggested that it was due to the effect of the excessive heat upon the wet grounds, that it might be caused by the fine sand carried in the winds from the Sahara Desert, and that it was due to some inorganic constituent of the drinking water, the sulphate of lime being especially suspected. Others were more general in their theoretical explanations, and believed that the sores resulted from the unknown miasms of the locality. In 1875 Weber, believing that Biskra boil would prove to be an inoculable disease due to a parasite, sent a section of the tissue, preserved in alcohol, to Carter in India for comparison

with Delhi boil and such other investigations as he might choose to make. In these preparations Carter found fungi with spores. In 1880 Laveran studied the affection at Biskra, convinced himself that it was transmissible, believed it to be due to a bacterium, and suggested that the local mosquito might play an important part in the transmission of the virus. In 1885 Cunningham in India detected certain parasitic bodies, often enclosed in cells, which he believed to be stages in the development of a mycetozoal parasite belonging to the group of monadidae. In 1891 Firth, studying Delhi boil, confirmed the finding of Cunningham, and proposed to name the parasite *Sporozoön furunculosum*. It has been suggested in recent years that the organisms seen by Cunningham and Firth were actually what are now known as leishman bodies. About the same time, Boinet isolated from Oriental sore and obtained in pure cultures, an organism with which he claims to have inoculated men, horses, dogs, rabbits, and guinea pigs, developing in them lesions similar to those of Oriental sore. Duclaux, Chantemesse, and others, found in Oriental sore a micrococcus which was pathogenic to certain laboratory animals, especially the rabbit. Nicolle found, both in suppurating and nonsuppurating Aleppo boils, a streptococcus which he believed to be the cause of the disease. Certain other investigators came to the same conclusion.

The honor of discovering the actual cause of Oriental sore is conceded to an American, Wright, of Boston. On the twenty-eighth of July, 1903, a girl of nine years of age was admitted to the Massachusetts General Hospital. She had on her face a typical Oriental boil. She was a native of Armenia, had been in this country only a short time, and had developed the sore about two months before she left Armenia. Greenough, into whose service the child was admitted, excised some of the tissue and turned it over to Wright for examination. The best preparations were obtained by fixation with pure methyl alcohol and coloration by Wright's modification of Romanowsky's stain. The bodies which attracted Wright's attention were generally round and measured from two to four microns in diameter. The striking thing in these bodies was the presence in each of two chromophil masses, one large and the other small. The larger was usually round with a diameter from one-fourth to one-third that of the parasite. The smaller mass was rod shaped and was found to take the stain more freely than did the larger mass. These parasites were found to be very numerous in smears made from the tissue. Wright's report was excellently illustrated by microphotographs and his demonstration was satisfactory in every way. He proposed to name this organism *Helcosoma tropicum* (tropical boil or sore). It is worthy of note that Wright's publication appeared in the same year as did those of Leishman and Donovan. It is evident from their first descriptions that these three men had found parasites which are at least morphologically identical.

Since Wright's discovery this parasite has been found in cutaneous leishmaniasis in practically every country in which this disease is endemic—in India, Turkestan, Abyssinia, Sudan, northern Africa, the Mediterranean Islands, and the Mediterranean Coast of Europe. The identity of Wright's organism and that of Leishman and Donovan, so far as their morphology is concerned, seems to have been fully established. The name given by Wright to his organism was for a while changed to *L. tropica*, but, as we have just stated, *L. tropica* and *L. donovani* are now regarded as morphologically identical; notwithstanding this, they produce two quite distinct diseases. Castellani and Chalmers say:

“Kala-azar infection in dogs affords immunity against *L. tropica* during and after the attack; Oriental sore protects monkeys partially or completely against *L. donovani*.”

It is interesting to note in this connection that there is a statement occurring here and there in the literature of this disease that the Jews of Bagdad formerly inoculated their children with matter taken from an Oriental sore in order to protect them against this disease.

Geographical Distribution.—In discussing the geographical distribution of kala-azar, we pointed out that in most endemic areas that disease and cutaneous leishmaniasis or Oriental sore do not occur in the same area, with an exception in southern Italy and Sicily. Aleppo boil is quite common in the city whose name it bears, less common but still existent in the country roundabout, extending over Palestine, in the Caucasus, the Transcaucasus, Persia, and Turkestan. In Teheran the disease is frequently seen in both men and dogs. In Mesopotamia it is found in villages, in the valleys of the Tigris and Euphrates, but most abundantly in the City of Bagdad. Laveran says that the “pendeh sore,” so-called from an oasis in Transcaspania, is identical with Oriental sore. According to Yakimoff, cutaneous leishmaniasis is very frequent in Turkestan, with its trade centers of Boukhara, Samarcand, and Askhabad.

We have already referred to the severe outbreak of Oriental sore in the French garrison at Biskra in 1844. Since that time endemic areas of this disease have been found widely distributed throughout the southern portions of those African provinces occupied by the French. These endemic areas are small and widely separated. For the most part they are oases in the great desert, some of which are those of Tuggart, 320 km. south-east of Biskra; of Laghouat, 360 km. south of Algiers, and of Ouargla, 800 km. southeast of Algiers. Only isolated cases are seen in the northern parts of Algiers and Tunis and most, if not all, of these have visited some endemic locality farther south. French students of the two forms of leishmaniasis found in Algiers and Tunis are inclined to the opinion that kala-azar is endemic only in places north of the thirty-fifth parallel, while cutaneous leishmaniasis is endemic only in places south of this parallel.

In Egypt, Oriental sore, under the name of Nile boil, is seen at Cairo and Suez. In Abyssinia this disease is reported to be quite frequent and the specific organism has been demonstrated in the tissue.

Sporadic cases have been reported in Greece and Italy. In Italy and Sicily the apparent antagonism so far as geographical distribution is concerned, so apparent in India and northern Africa, is not observed. Cutaneous leishmaniasis, along with true kala-azar, is reported from time to time in various cities in Sicily and along the Calabrian Coast in Italy. The existence of this form of leishmaniasis in the East Indies and in the Malay Archipelago is still a matter of doubt. Strong studied a sore in a native woman of Manila and he found bodies bearing some resemblance to Wright's parasite, but he was not able to convince himself that this was not due to a blastomycetie organism. American leishmaniasis will be discussed in the next section.

Seasonal Influence.—In northern Africa the seasonal influence on the development of new cases of this disease seems to be quite uniform. At Biskra and other endemic centers new sores are most in evidence after the extreme hot weather of summer is past and as fall comes on. Laveran says:

“The influence of season on endemic Oriental sore is very constant and remarkable; it is principally the months of September and October that the disease appears; it prevails with more or less frequency during the remainder of the year; but after February new cases are seldom seen.”

Numerous other French authorities make practically the same statement. In the Caucasus most cases develop in September and October. Writing of “pendeh boil” in the Transcaspian, Heydenreich says that this affliction is most in evidence in the summer months—July, August and September. In India the cold season apparently favors the development of the disease. In a French expedition sent into central Asia in 1885 and which terminated in the Battle of Kuschka, in some companies the percentage of soldiers infected with Oriental sore was from eighty-eight to one hundred.

Susceptibility.—Race apparently is without influence upon susceptibility. Social conditions are likewise without effect. In garrisons, both privates and officers are equally involved. At Delhi, Lahore, and Cambay, the higher caste natives are apparently just as susceptible to this disease as their inferiors, notwithstanding the fact that the former live under better sanitary surroundings. Apparently it is only necessary to enter an endemic area in order to be infected. Weber states that French officers, also tourists, arriving at Biskra in October or early November, are likely to develop the disease after a few days, while those arriving in late November or December are less likely to quickly acquire the disease. According to Hussenet, a company of men arrived at El Guettar on the

ninth of September, 1883, and nearly all of these soon had the sore, while a battalion arrived in the same locality at the end of November and no man in this company was infected.

Transmission.—As we have already stated, this disease has been experimentally induced by direct inoculation and it is auto-inoculable. According to Laveran, the slightest wound received while sojourning at Biskra during certain months is quite likely to be followed by the development of Oriental sore. It seems that in certain localities, like Aleppo and Biskra, the infectious material is so widely, so abundantly, and so uniformly attached to everything animate and inanimate that a break in the continuity of the skin is the only accident necessary to the acquirement of the infection. There can be scarcely a doubt that any insect which inhabits or even occasionally visits the cutaneous surface of man may be the carrier of this infection. It is not necessary that this insect be a biting one, provided an opening into or through the skin has already been made. Quite naturally, if the insect be able to inflict a wound on the skin and at the same time be the bearer of the virus the probability of infection is increased; in other words, this disease is spread from man to man by contact, which may be either direct or indirect. In certain localities man is not the only animal which bears these sores, the matter from which is widely distributed throughout the locality. In the history of his Journey to Aleppo in 1854, Willemin tells of dogs bearing the sores on their noses, as well as on other parts of their anatomy. One can hardly imagine a more efficient agent for smearing an infection over everything in a village or city than dogs, with infected running sores, possibly on their feet, legs, and especially on their noses. Similar observations concerning dogs with this form of leishmaniasis come from practically every known endemic area. Laveran is responsible for the statement that of 21 dogs picked up at random in a street in Teheran, 15 carried Oriental sores. These ulcerations were distributed over the body, the legs, the ears, the prepuce, the vulva, but especially on and within the nose. There is no doubt that in many localities the dog plays a large part in the transmission of this infection and from this animal, as from an infected fellow man, either by direct or indirect contact, a susceptible individual may acquire the disease. We would not imply that the dog is the only animal or agent engaged in the transportation and distribution of this virus. There are endemic areas in which the dog, especially the infected dog, is not greatly in evidence. Nicolle and Manceaux have made many experiments inoculating dogs with matter taken from Oriental sore on man. When these inoculations have been made on or within the nose or about the face, there is a period of about 36 days before an induration appears at the point of inoculation. This subsequently goes through all the stages observable in man. The testimony is that after complete recovery from one attack

of this disease or from the effects of one inoculation, the dog is subsequently immune to it. The cat is another children's pet and playmate which is naturally susceptible to the disease. Rats, mice, and guinea pigs are inoculable, but, so far as we know, there is no evidence that this disease ever occurs naturally in these animals. All the species of monkeys in northern Africa tested have developed this disease after inoculation. Nicolle and Manceaux inoculated without success donkeys, horses, sheep, rabbits, pigeons, and cold-blooded animals, such as lizards.

Bibliography

- MANSON, P.: Tropical Diseases, London, 1921, Cassell & Co.
NICOLLE, C., AND MANCEAUX, L.: Ann. de l'Inst. Pasteur, September, 1910.
RUSSELL, A.: The Natural History of Aleppo and Parts, London, 1756.
WRIGHT, J. H.: Jour. Med. Research, 1903, v, 472.

III. MUCO-CUTANEOUS LEISHMANIASIS

Leishmaniasis americana; *Espundia*

Description.—This disease is characterized by the appearance of one or more cutaneous sores, which are accompanied, or followed after long or short intervals, by ulcerations in the mucous membrane of the nose, mouth, and pharynx. The primary or cutaneous lesion or lesions may, according to Laveran, be ulcerous or nonulcerous. They may be single or multiple and usually there are only two or three, but Matta counted 51 distributed over the body of one patient. Since the virus is auto-inoculable, there is in most instances abundant opportunity for the development of multiple sores. They appear most commonly on the uncovered portions of the body and frequently they greatly disfigure the face, especially the lips, nose, and ears. The first thing seen is one or more erythematous dots resembling the bite of an insect and causing more or less itching. After from two to three days there appears within the erythematous spot a very small ulceration, which for a while grows and may attain a diameter of one inch or more. The borders of the ulcer show a bluish tint, while the surrounding skin is edematous, red, and painful on pressure. The surface of the ulcer is usually covered by a brownish crust, from the edges of which there exudes a stinking, serous fluid, often tinged or more deeply colored with blood. The adjacent lymphatic glands are at this stage enlarged and painful, but the pain soon disappears, while the glands remain larger than normal. As these ulcers develop there is evening fever and pain in the head and joints. The cutaneous ulcers develop slowly, usually persist for months, and in some instances continue for years. In most cases, however, after a variable period ranging from six months to two years, the cutaneous ulcers begin to cicatrize from the

periphery, thus healing and leaving permanent characteristic parchment-like cicatrices. The scarred tissue thus formed may leave permanent disfigurements quite as marked and quite as objectionable as those present during the active or ulcerative stage.

According to Tamayo, Escomel, and others, there are cases in which the cutaneous lesions do not ulcerate and the small tumor becomes a wart or a nest or group of warts. This form of American leishmaniasis is said to be quite prevalent not only among men, but among donkeys and horses, along the Amazon. Some of these papillomatous growths discharge small amounts of a highly fetid ichorous fluid. Matta described nodosities which resemble cauliflower and in which there is a marked tendency to hemorrhage. This type is said to be very persistent, continuing in some cases as long as from ten to fifteen years without developing ulcerative processes.

As a rule, to which there are exceptions, the mucous lesions do not appear until those on the skin are well developed or have undergone complete cicatrization. There are cases in which the initial lesion appears either on the mucous membrane of the nose or near the border line between the cutaneous and mucous membrane. According to Escomel, the cutaneous lesions heal or cicatrize and then, after an interval which may be of one or more years and during which the patient may be in fair health, the mucous lesions make their appearance. In most cases the mucous lesions are first recognized in the nose and their appearance is accompanied by a chronic coryza. More rarely, the first lesion appears on the palate, but whether first appearing in the nose or in the mouth, the disease process usually extends to the tonsils, the pharynx, and may involve the larynx, affecting the vocal cords. The development of this stage of the disease may continue through many years, even up to 30, render the victim miserable in himself and repugnant to all who see him. Fortunately, most patients before reaching or continuing long in this stage contract some intercurrent infection and die from it. Escomel says that he has seen patients die from espundia without intercurrent infection, but that this is rare.

In these ulcers, both the primary or cutaneous and the secondary or mucous, *Leishmania donovani* has been found. We, therefore, are justified in concluding that *Leishmaniasis americana* is a specific infectious disease, the causal agent of which cannot be distinguished, morphologically at least, from that found in kala-azar and in European cutaneous leishmaniasis.

History.—In certain parts of South and Central America diseases characterized by ulcerations of either the cutaneous or mucous surfaces, or of both, have been long known to exist and have been described under various names. There can be no doubt that in the voluminous literature

bearing upon this matter, three or four, possibly more, diseases, have been confounded. One observer has seen and described cases of leishmaniasis, while others have been concerned with yaws or framboesia, and still others have been dealing with blastomycosis. According to Tamayo, ulcerous diseases were in evidence among the natives at the time of the conquest of Peru and probably, as is indicated by pictures on water vases, long before that time. In 1840 Smith, and in 1846 Tschudi, described endemic cutaneous ulcerations seen in different parts of Peru, and especially on the road being built at that time from Lima to the mines of Cerro de Pasco. The natives at that time attributed the disease to drinking water. In 1885 Cerqueira and others reported a dermatosis in certain parts of Brazil which they believed to be identical with Oriental boil. About 1895 Breda, of Padua, Italy, studying Italians who had returned from South America, began to write quite voluminously upon a disease seen among these people, under the name of Bouba Brasiliana. Breda believed this disease to be due to a bacillus which he claimed to have isolated and with which he satisfied himself that he had successfully inoculated laboratory animals. There can now be scarcely any doubt that at least some of the cases which Breda studied were afflicted with American leishmaniasis. During the last decennium of the nineteenth century Darier, Christmas, Jeanselme, and others described, under various names, ulcerous diseases seen in Brazil and French Guiana, and in 1909 Carini and Paranhos demonstrated that the ulcers seen on workers in the construction of the North-eastern Brazilian Railway and locally known as the ulcers of Bauru (a Brazilian province) contained leishmania. This work was soon confirmed by Linderberg, who proposed that the disease should be called ulcerous leishmaniasis. The discovery that *L. donovani* can be easily cultivated in the Novy-McNeal medium has facilitated its detection and isolation by South American physicians. In 1912 Splendore came to the conclusion that so far as the causal agents are concerned there are two forms of Brazilian ulcer, one a leishmaniasis and the other a blastomycetic infection. This investigator detected some differences in the flagellated forms of European and South American leishmania. He believed the latter to be a strain or variety of the former and that the difference was sufficient to justify the designation of that found in the Western Hemisphere as *L. americana*. Other South American observers believe that there are in that country several species of leishmania. In 1911 Escomel did some valuable work on mucous ulcerations in Peru, where the disease is generally known as espundia. This investigator sent preparations to Laveran, who identified the organism as *L. tropica*, but with sufficient variation from this to warrant the name of *L. americana*. There can now be scarcely any doubt that both in Brazil and in Peru there are two endemic ulcerous diseases, one due to the leishman body, the other to a yeast. On the Canal

Zone, Darling and Connor have seen many cutaneous ulcers in which they have demonstrated leishman bodies.

Geographical Distribution.—The best known and most thoroughly studied endemic areas of American leishmaniasis lie in Brazil and Peru, although there are other centers in Yucatan (Mexico), Panama, the Guianas, Paraguay, and Uruguay. In Brazil the local names, or at least some of them, for this disease, are the following: Bouba or buba, Bauro ulcer, Bahia sore, and Avandhandava ulcer. Under these various names, endemic cutaneous and mucous ulcers are widely distributed throughout Brazil, but they have been most frequently observed among workers, especially those engaged in railroad construction in the virgin forests of that country.

The names for leishmaniasis employed in different parts of Peru are: Uta, espundia, jucuya, qeepo, and tiace-arana. The disease is most prevalent in the central zone of Peru, in a region where there is luxuriant vegetation and where it is hot and humid. Escomel found perfect specimens of espundia along the banks of the river Madre de Dios. Anderson found it at high altitudes, from 3,000 to 18,000 feet, where it was cold and wet. Strong and his colleagues observed it at Surco in a school for children located in a mountainous region. These observers state that at Surco and Otao a large proportion of the inhabitants as seen at that time (1913) showed either active stages of the disease or cicatricial evidence of having had it. It seems that the name of the disease (uta) in that locality is derived from that of the village Otao.

It is believed that this disease was introduced into Paraguay from Brazil, and in the former country it still carries the Brazilian name of buba. In Paraguay, American leishmaniasis is most abundantly seen among workers in the forests. In the three Guianas the local names are determined by the political divisions; English, forest yaws; French, pian-vois; Dutch, boshyaws. In this region new cases become more numerous with the approach of the rainy season and prevail from the last of November to the middle of April. It makes no distinction in color or race, but is most abundant among those whose occupations carry them into the forests. Sporadic cases have been observed in Argentina, Bolivia, Colombia, and Venezuela.

On the Canal Zone, Darling and Bates saw many cases of cutaneous leishmaniasis; two with ulcerations on the ears, and one in which the nasal mucous membrane was involved.

In Yucatan, the site of the disease is so frequently on the ear that it is known as ear ulcer. It is said to be common throughout the interior of Yucatan, in Campeche, and in Quintana Roo. One case has been reported in a creole in Martinique. Stevenel, who reports this case, thinks that it was contracted in the woods in the high altitudes of that Island. So far

as we know, it has not been reported as indigenous in the Greater Antilles or in the United States.

In Animals.—The evidence of an animal reservoir for the virus of this disease in South and Central America is not convincing. Dogs are inoculable, but there is no evidence that this disease has any wide prevalence naturally among dogs. Pedroso in July, 1912, in a village in north-western Brazil, where there was at the time a case of leishmaniasis in a man, found two dogs with nasal ulcerations, and in smears from one of these he demonstrated leishman bodies. The master of the second dog had a leishman ulcer on the foot and the dog licked this sore. From the facts and the appearance of the ulceration, Pedroso concluded that the ulcers in the second dog were also due to leishman bodies. Migone examined the cutaneous lesions of many dogs in endemic parts of South America, but was never able to identify leishman bodies in these animals. Brumpt and Pedroso in an epidemic area in Brazil saw five dogs with ulcers but were not able to demonstrate leishman bodies in these. It is said that the dogs of workers in the forests of Brazil are ferocious and not easily handled. Cats and monkeys are inoculable, but are not known to have this disease naturally.

Transmission.—It is both the popular and professional belief that American leishmaniasis is transmitted by some biting insect whose favorite habitat is in the virgin forests, but there are so many insects in these regions and the sore is so slow in developing that it seems a hopeless task to pick out the guilty one. All kinds of flies, gnats, and mosquitoes have been suspected. The natives of the Canal Zone accuse a fly known as *Mosca boyana*. This fly feeds largely on the yellow flowers which give it its name and which grow in the jungles. Brumpt and Pedroso, after reviewing the insects possibly concerned in the transmission of this virus, arrive at the conclusion that certain tabanid flies are most likely the guilty agents. In the valley of Convencion in Peru the popular opinion is that the disease is disseminated by a gnat. Townsend, studying the disease in certain sections of the Peruvian Andes, thinks that there are two species of ants concerned in the distribution of the virus. He found leishman bodies in the intestines of these insects. He was unable to find these bodies in the proboscis or salivary glands and he came to the conclusion that the virus is not transmitted through the bite of the ants, but is deposited from the bowels onto the skin while the ant is biting and inoculation results from scratching. Laveran points out that it is not necessary to assume that the transmission of this virus is in all instances at least, due to a biting insect. Any insect which rests upon man may mechanically carry the virus, deposit it onto the skin, and inoculation may result from scratching. Among the workers in the forests of Brazil and Paraguay it has been observed that soon after the arrival in the camp of one bearing a leishman sore others in the party develop like sores. Seidelin

tells of a man who had an ulcer on his right ear and who was accustomed to sleep with his right hand under his head, as a result of which an ulcer appeared on the arm where it came into contact with the ear. There is a popular opinion among the peons of Paraguay that the rattlesnake is a reservoir for this virus and that it is transferred from the snake, especially from the body of one that has been killed, to man by an insect believed in this country to be a tick.

So long as the sores of *Leishmaniasis americana* are confined to the skin there may be difficulty in distinguishing it from Oriental sore, but the former is more persistent and is followed by the appearance of sores on the mucous membranes, which, if it occurs at all in Oriental sore, is extremely rare. In South America there has been much confusion between the lesions of leishmaniasis and those of blastomycosis.

Prevention.—Since we do not know the transmitting agent or agents in this disease, it will be necessary in discussing its prophylaxis to speak tentatively and in a general way. There is no satisfactory reason for believing that this disease is due to insanitary local conditions. A healthy individual makes a journey through what is practically a virgin forest and in doing so acquires the infection. If we are to believe the case reports, and there is no reason for doubting them, it is not necessary that this individual should on his journey come into contact with any other human being or rest where man has ever been before. If these things be true, then there must be some reservoir of this virus in the forest and there must be at the same time in the same location insects which bear this virus to the traveler. It is said that the woodsmen in Paraguay are learning to protect themselves from insects by every possible means. They wear gloves, protect their arms and faces by netting, and the more intelligent rest at night or take their siesta by day only under mosquito netting. Protection by these means is not, however, so efficient as it is in malaria. It would be difficult to so clothe a working woodsman that he might do efficient work and at the same time have his entire cutaneous surface protected absolutely from insects. Ants, ticks, mites, and various other creeping and crawling things, are likely to find their way under the clothing however skilfully it may be arranged.

Bibliography

- ANDERSON, D. E.: International Medical Congress, London, 1913.
 BATES, L. B.: Jour. Am. Med. Assn., March 22, 1913.
 DARLING, S. T.: Arch. Inter. Med., May, 1911.
 DARLING, S. T., AND CONNOR, R. C.: Jour. Am. Med. Assn., April 29, 1911.
 ESCOMEL, E.: Soc. de path. exotique, July 12, 1911.
 LAVERAN, A.: Leishmanioses, with full reference of literature to date, Paris, 1907.
 MIGONE, L. E.: Trans. Soc. Trop. Med. and Hygiene, June, 1915.
 SMITH, J.: Edinburgh Med. and Surg. Jour., 1840.
 STRONG, R. P., AND COLLABORATORS: Report of First Expedition to South America, Cambridge, 1913.
 TAMAYO, L.: La uta en el Peru, 1908.

CHAPTER XXVII

TETANUS

Lockjaw; Trismus

Description.—This is a specific infectious disease caused by the toxin of *Bacillus tetani* and characterized by severe convulsive contractions of the voluntary muscles. In man, the muscles first affected in the majority of instances, are those which close the jaw (the masseters). The convulsive seizures spread downward over the body and limbs until in severe cases every muscle in the body is involved. This form of the disease is known as descending tetanus. In the lower animals, much more rarely in man, tetanic symptoms originate in, and for a time are confined to, that part of the body bearing the wound through which the bacillus has been introduced. From these muscles the seizures extend to more distant parts of the body and may involve the whole muscular system. Formerly, it was customary to speak of idiopathic and traumatic tetanus. The latter term was used when the disease followed some recognizable injury. It is now known that the bacillus enters the body only through injured cutaneous or mucous surfaces; therefore, all tetanus is traumatic. It still remains true that in some cases no injury is recognizable. The wound on the skin may be so trivial as to attract no attention when received and so thoroughly healed before symptoms appear that there is no certain recognition of its existence. The bacillus is a frequent invader of the alimentary canal and occasionally finds its way into the air passages and through either of these avenues it may penetrate the tissues. The toxin combines with the nerve cells in the spinal cord and the muscular spasms result from the injury thus done to these cells.

In the great majority of instances the contractions of the extensor muscles greatly overbalance those of the flexors, and the body, both as shown in its members and in the trunk, is extended. In severe seizures the limbs are extended and rigid, while the head is drawn backward and only the occiput and the heels touch the bed. In less severe cases, there is a tendency to assume this rigid position. This is known as opisthotonos. This is the position usually assumed by the body in this disease. In very rare instances the head and the shoulders are brought forward and the body is bent upon the abdomen. This is known as emprosthotonos. In these instances the contraction of the abdominal muscles is sufficient to overcome the extensors. Still more rarely, the

body is bent to one side or the other. This is known as pleurothotonus. The muscular spasms characteristic of this disease vary from the barely perceptible twitching to actions so forcible that vertebral processes are broken and the teeth crushed by the closure of the jaws. As a rule, the intellect remains unaffected during the disease. In most cases the temperature does not attract attention, although in exceptional instances it may run to 104° and over. It has been observed that the temperature may continue to rise for from 20 to 40 minutes after death. The mortality from the disease is high and without specific treatment generally runs from seventy to eighty and occasionally to ninety per cent. Death from asphyxia is the most frequent form, though exhaustion and cardiac failure occasionally terminate the case.

History.—Excellent descriptions of this disease, with recognition of its high fatality, are to be found in the writings of Hippocrates, Aretaeus, Galen, Caelius Aurelianus, and other Greek and Roman authorities. It is also described accurately and certainly by Arabian physicians of the ninth and tenth centuries. The chief theory concerning its causation has attributed the disease to sudden changes in weather, with exposure to wet and chilling of the body. As late as 1886 Hirsch, after an exhaustive study of the geographical distribution of this disease, wrote as follows:

“There is no question that the affection of the central nervous system, which is conspicuous among the phenomena of tetanus, may be produced by a variety of external causes, and probably by internal causes also; and that among these, wounds play a prominent part. But none of the external agencies has a more decided significance in the etiology, none comes more to the front as a real decisive factor in the pathogenesis, than certain *atmospheric influences*, which determine the distribution of tetanus over the globe no less than its predominance at certain seasons and under certain kinds of weather. All observers who have had practical experience of tetanus in various latitudes are agreed in saying that the disease is commonest in the tropics, and that, as a general rule, it becomes less frequent the farther the *climatic circumstances* of the locality diverge from tropical climate. Those experiences of individuals are entirely in agreement with the sketch of the distribution as given above, which shows a decreasing frequency from the equator to the poles. That the height of the *temperature* is not the essential thing here, is shown by the fact that the largest number of cases in the tropics, according to nearly all the authorities, does not fall in the hot season but in the season preceding the rains, and corresponding to our spring, or in the cool season following the rains.”

Elsewhere the same author adds:

“*Chill* was given as a frequent cause of tetanus by the ancient and medieval physicians, such as Hippocrates, Aretaeus, and Avicenna; and although opinions have fluctuated a great deal as to the nature and genesis of the disease, that experience has been substantiated to the fullest extent by observers in all subsequent periods, including those of the present time.”

Ever since man has engaged in destructive combat with his fellow,

tetanus has been regarded as one of the horrors of war. There are, however, no reliable statistics concerning its occurrence and fatality in different wars. Larrey, Napoleon's great physician, records the high prevalence and great mortality of this disease in the Egyptian campaign (1799-1801). In the Crimean War, out of 12,094 wounded English there developed nine cases of tetanus, or .75 per 1,000. In our own Civil War, out of 246,172 wounded there were 505, or a little more than two per 1,000. In the Franco-Prussian War, among 95,000 wounded there were 350 cases of tetanus, or 3.5 per 1,000. In the Russo-Turkish War, out of 51,700 there were 66 cases of tetanus, or 1.2 per 1,000. Concerning tetanus in the World War, we shall speak later.

Most writers on tetanus emphasize its importance in war as evidence of its most destructive action and highest mortality. This is not true. There is a form of tetanus which has destroyed ten and possibly a hundred for every soldier who has died from this disease. We refer to the tetanus of the newborn, or, as it is scientifically designated, tetanus or trismus neonatorum. Writing of the prevalence of this disease on the Island of Cayenne, Bajon says:

"There is perhaps no country where children are so difficult to rear as in Cayenne. They have hardly emerged from their mother's womb to the light of day when they fall, in large numbers, into a state of spasm, which by and by locks their jaws and makes the whole body as stiff as a bar of iron."

Of the prevalence of this disease in British Guiana, Hancock (1831) wrote:

"It is so frequent and fatal in the colonies of Essequibo and Demerara, that, at an average estimate, it kills half of the whole number of infants which are born there."

Like high death rates from this form of tetanus prevailed during the first half of the nineteenth century over large parts of Brazil, Argentina, and other South American countries. One author states that at that time one-fourth of all the children born in Rio de Janeiro died from this disease. A fearful mortality was reported from Montevideo in 1852. In 1856 four per cent of all deaths in Charleston, and 3.7 per cent of all deaths in New Orleans, were due to tetanus neonatorum. Watson, writing of the prevalence of this disease among the negroes of Tennessee before the Civil War, said:

"When called to see their children we find their clothes wet around their hips, and often up to their armpits, with urine. The child is thus presented to us, when, on examination, we find the umbilical dressing not only wet with urine, but soiled likewise with feces, freely giving off an offensive urinous and fecal odor combined at times with a gangrenous feter, arising from the decomposition, not desiccation of the cord."

About the same time Grier wrote:

"When the disease appears endemically on a plantation it may be arrested by having

the negro houses whitewashed with lime inside and out, by raising the floor above the ground, by removing all filth from under and about the houses, by paying particular attention to cleanliness in the bedding and clothes of the mother and in dressing of the child."

In times of slavery, in our southern states many a plantation mistress took it upon herself to first dress the newborn negro child and to make daily or more frequent visits to the lying-in mother and her charge. More than this, in some households the daily bathing of the newborn negro children on the plantation was carried out under the supervision of the mistress of the house.

Epidemics of trismus neonatorum during past centuries were not confined to negroes, but occurred from time to time in the most renowned lying-in hospitals in Europe. There were born in the Dublin Rotunda from 1757 to 1782, 17,650 children, 2,944, or more than sixteen per cent, of whom died from tetanus. Clark, who reported these conditions in the Rotunda, undertook to improve them and was greatly rejoiced when he reduced the mortality from this disease to five per cent. In a lying-in hospital in Stockholm, tetanus neonatorum killed 42 out of 505 children born in that institution in 1834. According to Finsen, during some years in the early part of the nineteenth century, two out of every three children born on Grimsö, a small island off the north coast of Iceland, died from tetanus.

It was through the study of tetanus neonatorum that the profession was first impressed with the idea that this is an infectious disease. We quote again from Hirsch:

"The doctrine that tetanus neonatorum is very often to be interpreted as *traumatic lockjaw*, is borne out by the fact that it mostly appears between the sixth and twelfth day after birth, or during the period when the detachment of the fragment of umbilical cord is proceeding; and the opinion often expressed, that bad treatment of the umbilical cord after the birth is a contributory cause, is not to be summarily dismissed as improbable. Another operation that has often given rise to trismus neonatorum is circumcision of Jewish and Mohammedan infants. * * * There is, however, another point to be considered here, to which I have already referred and on which I should be inclined to lay special stress for the production of trismus neonatorum. I mean *bad hygiene*, which would set up *infection* in the newborn infant all the more readily that the umbilical surface offers an easy way of entrance to infective matters. Among the authorities on lockjaw in the newborn, there is but one opinion that the disease is almost confined to the crowded and filthy dwellings of the poor, or to badly kept foundling and lying-in hospitals, breaking out in the latter whenever the insanitary state arises as a result of overcrowding or of an epidemic of puerperal fever, or the like. All practitioners who have seen the disease in the tropics are agreed that, next to chill, one of the most potent causes of trismus neonatorum is the neglected and filthy state of negro dwellings, which baffles all description and reaches its height at the time of confinement. A number of observers in temperate climates have held the same language regarding the effect of filth in the production of trismus."

It must be evident from the above that when we speak of a wound as being essential to the development of tetanus we must have a broad interpretation of what the term "wound" means. Tetanus neonatorum is undoubtedly due to infection through the severed umbilical cord. Ignorant people are likely to tie the cord with anything which comes handy and as likely as not it will be some highly infected thing. Then the cord is dressed, if at all, with some highly infected article. When we speak of wounds and tetanus we must bear in mind that the wound is not necessarily a break in continuity inflicted by some weapon or by accident; it may be simply due to altered tissue. Apparently, it required some months to call this fact to the attention of the medical officer in the late World War. In trench foot there is no wound or there may be no wound, but the tissue is so altered that it is easily penetrated even by organisms possessing but a moderate degree of motility. It was only after many cases of tetanus had occurred in trench foot that this avenue for the admission of the tetanus bacillus was recognized, and thereafter trench foot was treated prophylactically as were other wounds. In this connection, the following quotation from Bruce is interesting:

"At the beginning of the war orders with regard to the prophylactic injection of antitetanic serum were frequent in connection with wounds, but it was not recognized that trench foot was a wound. One day it was found that, within a fortnight, 15 cases of tetanus originated in cases of trench foot in which no one thought that prophylactic antitoxin was necessary. The 15 cases made the surgeons open their eyes."

About the middle of the nineteenth century it was evident that the idea of tetanus being an infectious disease was growing in the medical mind. In 1854 Simpson believed that a strychnin-like substance is formed in the wound, and in 1859 Betoli concurred in this belief and suggested that the poison might result as the product of fermentation. From 1868 to 1870 numerous attempts were made to induce tetanus in animals by injecting blood or blood serum of man while suffering from this disease. It should be understood that all experiments of this nature failed and would do so today. In 1882 Nocard reported an epidemic of tetanus among young horses, all of which were castrated with the same instrument without sterilization. This observation led Nocard to inoculate sound animals with nervous tissue taken from the sick. This quite naturally failed. In 1884 Carle and Rattone inoculated a number of rabbits with material taken from an acne pustule on a man who was suffering from tetanus and induced the disease in all these animals. They went further and demonstrated that the disease could be perpetuated by repeated transfer from the wound of one animal to that of another. In 1885 Nicolaier, having been struck with the frequency with which gardeners acquire the disease after slight injuries to their feet

and legs, inoculated with garden soil large numbers of white mice, rabbits, guinea pigs, and dogs, and in all of these with the exception of the dogs, tetanus developed. Later experiments have shown that the dog also is susceptible but requires larger inoculations than the other animals. Nicolaier was able to demonstrate in the pus of his wounded animals bacilli which were characterized by being distinctly drum-stick shaped. Quite naturally, he came to the conclusion that the strychnin-like poison of Simpson and others was generated in the wound by this characteristic-appearing bacillus. Within the next year or two the experiments and observations of Nicolaier were repeated and confirmed in Germany by Rosenbach and in France by Nocard. The last-mentioned investigator transferred tetanus from a sick horse to a sound one while castrating the latter and demonstrated the bacillus of Nicolaier in the wounds of both.

In 1889 Kitasato, recognizing the fact that the enlargement at one end of the bacillus of Nicolaier represents a spore, heated these cultures to 80°, at which temperature the nonspore-bearing germs of all kinds were destroyed while spores of tetanus remained, and when subsequently placed at proper temperature grew into bacilli. In this way Kitasato obtained a pure culture of the tetanus bacillus. In 1890 Faber showed that filtered cultures of the tetanus bacillus from which all organisms had been removed induce the disease in animals, and about the same time Behring and Kitasato prepared a tetanus antitoxin and experimentally demonstrated its value.

The Bacillus.—The bacillus of tetanus is a rod from 4 to 6 microns in length and from .3 to .4 micron in breadth. Without spores, there is nothing distinctive in its appearance, but in cultures it sporulates in a few hours and then it appears as short rods bearing a ball-like enlargement at one end and forming the drum-stick appearance quite characteristic of this organism. In the culture within a relatively short time the rod disappears, leaving only the spores. It is anaerobic and when grown under this condition it demonstrates slight mobility which, of course, is not observed in the spores. The bacilli are gram-positive and take the ordinary basic anilin dyes. In the sporogenous form the stain is limited to the rod with a rim about the spore. The spore of this bacillus is highly resistant to external agents. It bears without harm a temperature of 80° C. for six hours and may resist boiling for four or five minutes. For the sterilization of cultures a temperature of 110° for from five to ten minutes is necessary. The spores are not destroyed by exposure to 5 per cent carbolic acid or 1 per 1000 corrosive sublimate. Their full virulence after being kept dried for two and one-half years on splinters of wood has been demonstrated.

Bacillus tetani is widely distributed over the earth. It is found al-

most constantly in the intestinal contents and feces of herbivorous animals, especially of horses, and in a variable but considerable percentage of men. There are certain soils which are unusually rich in this organism; such are known as tetaniferous soils. These are lands which have been enriched by animal manure. It will be evident from this that the danger of wound infection from soil is widely variable in different localities. The highly manured soils of Belgium and northern France account for the large number of cases of tetanus which developed from war wounds received in these countries. In previous wars it had been observed that the number of cases and the mortality from tetanus varied greatly on different battle fields. We have already referred to the experience of Larrey in the Egyptian campaign of 1799-1801, and it may be stated that this surgeon met with a similar experience in Austria in 1809. According to Thierry, 110 cases of tetanus were reported on one day after the Battle of Bautzen (1813), the wounded having been left overnight after the battle on damp ground and having their wounds badly soiled. That the tetanus bacillus varies widely in its distribution in the soil has been shown by the geographical distribution of cases of tetanus in civil life. A few years ago when so many cases of tetanus followed Fourth of July accidents, it was evident that tetanus more frequently accompanied such injuries in certain localities. In the United States, Pennsylvania, the Hudson River Valley, and Long Island are known to be areas in which the soil is rich in tetanus spores. A like observation has been made concerning the frequency of tetanus in the lower animals, and especially in horses.

There is another soil condition which greatly influences the chances of tetanus infection. We refer to the presence in the soil of other bacteria, such as staphylococci and streptococci, and especially certain anaerobes, as *B. welchii* and *Vibrio septique*. If tetanus spores be freed from all their toxin and from the presence of all other bacteria and injected into the healthy tissue of an animal they do not cause disease; in other words, the tetanus organism will grow, multiply, and produce its toxin in the animal body only when in the presence of some other organism or when the tissue has been rendered necrotic by some other agent. Courmont and Doyon showed that as many as 2,500 spores of the bacillus of tetanus freed from all toxin and all other microorganisms could be injected into the tissue of a guinea pig without any resulting harm. The same investigators came to the conclusion that without the protection furnished by its toxin or the presence of other bacteria, the tetanus spores are destroyed by the phagocytes, while in the presence of these helpful agents they are protected. Tetanus spores are present in many wounds which are not accompanied by the development of symptoms of tetanus. Tulloch, in a series of wounds studied in the

late war, found tetanus spores in twenty per cent of those who did not develop the disease. Such organisms as *B. welchii* and *Vibrio septique* favor the action of tetanus spores by devitalizing the tissues. In a healthy granulating wound tetanus spores, although they may be present, will not cause tetanus. The importance of cleansing every wound, removing so far as possible all traces of foreign matter and all dead or dying tissue, was not fully realized until the World War made it evident in many hospitals. The excision of the wounded area became the common procedure and, with the prophylactic employment of tetanus antitoxin in all wounds, came very near eradicating tetanus before the war closed.

In nearly all instances the tetanus bacillus is carried into a wound as a spore and, as we have seen, these spores outside the body may continue in their state of potential virulence indefinitely. This is equally true of them after they have been introduced into the tissues. They may continue in partly healed wounds, in carious bones, or in scar tissue, retaining potential virulence quite indefinitely and capable of being awakened into activity by any condition which devitalizes the tissues in which they lie. It is the accepted idea that tetanus is not a systemic infection but a local one, which it continues to be, and that the organism or the spores manufacture the toxin which constitutes the harmful agent.

By serologic tests, Tulloch divides tetanus bacilli into three types. Up to the present time this seems to be of no practical value, since all of these types produce the same toxin and with this, quite naturally, the same antitoxin is obtained. Tulloch thinks it possible that there may be in the antitoxins antibacterial properties and that these may vary with the type.

The Toxin.—As we have already stated, the toxin was first prepared and studied in 1889 by Faber, who obtained it by the filtration of cultures through porcelain. In the same year, Tizzoni and Cattani confirmed and extended the findings of Faber, which were shortly afterwards made more definite by the contribution of Vaillard and Vincent. What we call tetanus toxin is a filtered culture of the tetanus bacillus, and the presence and properties of the specific poison contained in these cultures have been demonstrated experimentally. No toxin has been obtained in a pure state and, consequently, we remain wholly ignorant of the chemical composition of any and all toxins. The tetanus toxin is soluble in water, is nondialyzable, is precipitable with alcohol, and is destroyed by mineral acids. Its virulence rapidly decreases on exposure to air, but it may be kept without marked deterioration quite indefinitely when covered with oil and placed in the dark. When heated to 65° C. it begins to lose its toxicity, but its destruction at this

temperature is slow and incomplete. At 80° C. it loses its virulence entirely within a few minutes. It may be precipitated by the addition of from 10 to 15 volumes of absolute alcohol to the filtered culture. The alcoholic precipitate when redissolved in water is found to be possessed of all the virulence of the original filtered culture. Tetanus toxin is a highly lethal substance, even in its impure state, which is the only form in which we know it. Of a given filtered culture, one one-millionth of a cubic centimeter may kill a white mouse; one ten-thousandth cubic centimeter, a guinea pig; one-fourth cubic centimeter, a rabbit; one-half cubic centimeter, a frog; two cubic centimeters, a horse; four cubic centimeters, a dog; ten cubic centimeters, a chicken. Figuring out as to the killing power of one gram of body weight, the horse is the most susceptible of experimental animals. From observations, man seems to be quite as susceptible as the horse.

There is always a period of incubation between the injection of toxin and the development of symptoms. This period of incubation can be shortened but not obliterated by increasing the size of the dose; in other words, tetanus toxin, whatever the size of the dose, whatever the avenue of administration, is incapable of immediately inducing symptoms. For instance, Courmont and Doyon injected intravenously into a dog one hundred times the fatal dose and the first symptom developed after 20 hours.

The distribution of tetanus toxin through the body and its action on the tissues were some years ago believed to be definitely settled by the experimental work of Meyer and Ransom. We give the following résumé of this theory as recently stated by Ransom:

“When tetanus toxin is injected subcutaneously it begins at once to pass from the lymph spaces into the lymph vessels and can, after a few minutes, be recognized in the lymph of the thoracic duct. By this route it reaches the blood stream, not much being taken up by the blood vessels direct from the seat of injection. The distribution then goes on till, in about 24 hours, the lymph and the blood contain per cubic centimeter about the same amount of toxin. If the toxin is given intravenously it soon begins to pass into the lymph, and again after some 24 hours the thoracic lymph and the blood serum contain per cubic centimeter nearly equal quantities of toxin. Neither after subcutaneous nor after intravenous injection can toxin be detected in the cerebrospinal fluid, not even when very large doses of toxin far exceeding the minimal lethal dose have been given. If by means of lumbar puncture the toxin is injected into the sub-arachnoid space without injury to the pia or cord it passes rapidly into the blood stream, and after the usual period of incubation general tetanus ensues. If, however, the toxin is injected intravenously and immediately afterwards the spinal cord is injured by the injection of a drop of normal salt solution, then the general tetanus is preceded by a local tetanus in the muscles corresponding to the injured segment of the cord. If the injection of toxin is made direct into the cord a local tetanus corresponding to the injured cells ensues, and the period of incubation is greatly shortened. If an animal is first protected by the administration of a large dose of antitoxin so that

no free toxin can exist in the blood, and then a small dose of toxin is injected into a motor nerve, a local tetanus corresponding to the distribution of the injected nerve results. Injection of toxin into a purely sensory nerve does not cause either local or general tetanus.”

It will be seen from this quotation that the generally accepted belief is that the toxin is transported along the motor nerves from the wound to the central nervous system. The cells of the cord, for instance, are not supposed to combine with the toxin brought to them through the blood or lymph and are affected or attacked only by that toxin which comes to them through the motor nerves. The toxin, having reached the cord through a given motor nerve, extends from segment to segment until finally the cord is sufficiently involved to give rise to the characteristic symptoms of the disease. Ransom says:

“The progress of events seems to be: The toxin traveling along the motor nerves reaches the corresponding motor cells and sets up there a certain overexcitability, so that the usual normal reflex impulses which maintain the normal muscular tone become more effective, the tone of the muscles concerned is increased, they acquire a more or less distinct rigidity (stiffness), and freedom of movement is diminished. This is in animals the first symptom of tetanus, and with small doses of toxin nothing further may occur; there is no increased reflex, and the whole symptom may pass off in a day or two or even in a few hours. If the dose of toxin has been somewhat larger its action extends to receptor cells in the reflex arch in immediate connection with the affected motor cells; they become overexcitable, so that tactile excitement of the affected (tetanic) limb causes increased response in that limb, but not elsewhere. In animals a flexion reflex is thus often converted into an extension. In the jaws of man this increased reflex excitability causes the inhibitory impulse which is necessary to open the jaws to be converted into an augmentor impulse closing them. If, as happens not infrequently in human beings, the diaphragm is very early attacked (before the jaws), then respiration will be to some extent interfered with because the inhibitory relaxation of the muscle tends to be converted into a contraction (pain in the chest). For a similar reason, if the muscles of the soft palate and glottis are early affected, difficulty in deglutition may be, and, in fact, often is, a very early symptom. Often before the exaggeration of the reflexes becomes excessive there are frequent clonic contractions, twitchings of individual muscles in the vicinity of the point of injection or the infected wound, indicating increased reflex excitability. After large doses of toxin, more and more motor cells and more reflex apparatus in the cord gradually become affected; there is a general rise of muscular tone and general increase of reflexes.”

The Antitoxin.—Tetanus antitoxin, discovered by Behring and Kitasato in 1890, is prepared much in the same way and on the same principles as diphtheria antitoxin. There are two standards in determining the value of tetanus antitoxin. The U. S. A. unit, officially adopted in this country and practically used by all the allied nations in the World War, is that amount of antitoxin necessary to preserve the life of a 350-gram guinea pig for 96 hours when mixed with 100 minimum lethal doses of the toxin and injected subcutaneously. One German unit, gen-

erally written 1 A. E., is equivalent to 40 U. S. A. units. The minimum lethal dose of the toxin used by the U. S. Public Health Service in standardizing the antitoxin is 0.000006 gram and the test dose for the standardization of sera (100 minimum lethal doses) is 0.0006 gram. Madsen, of Copenhagen, President of the Provisional Health Committee of the League of Nations, has taken steps to secure the international standardization of all antitoxins.

There is some advantage in the preparation of antitoxin in having a powerful toxin. For this purpose, the bacillus is frequently grown in a glucose broth, slightly alkaline, and containing a piece of sterile tissue. London, working in Petrograd in 1917, reported that by precipitating a filtered culture with a seventeen per cent ammonium sulphate solution he obtained a toxin which killed white mice in two days in a dose of 0.00000002 gram.

Tetanus in the World War.—When the World War began on the Western Front, tetanus antitoxin was not employed prophylactically in any army. The percentage of the wounded who developed tetanus was large and the percentage of deaths among the cases was also large. In the English Army the incidence of cases of tetanus per 1,000 of wounded reached its highest point in September, 1914, and included those who were injured at the Battle of Mons and at the Battle of the Marne. In October, 1914, the incidence declined slightly, as shown among those wounded at La Bassée and Ypres. About this time prophylactic doses of tetanus antitoxin were administered to all the wounded. As a result of this, or at least following it, these facts in regard to tetanus were observed: (1) The percentage of the wounded who developed this disease markedly decreased. (2) The period of incubation or the time elapsing between the receipt of the wound and the development of first symptoms was prolonged. (3) The percentage of deaths among cases was decreased. In the English Army during 1914-1915 there was an average incubation period of 13.4 days, while from December, 1917, to April, 1918, the average period of incubation was 46.2 days. Bruce says that the case mortality rate was lowered from 85.0 to 44.3 per cent, and he attributed this in large part to the prophylactic employment of antitoxin. At first the prophylactic dose employed in the English Army consisted of 500 U. S. A. units, but this was increased to 1,500 units. There is some doubt as to the benefit to be attributed to this increase. The first dose, administered as soon as possible after the infliction of the wound, was repeated weekly until the wound was entirely healed. It is generally believed that whatever the dose of antitoxin administered, practically all of it has been eliminated from the body within a week. MacConkey says:

“If the dose of 500 units is repeated at the end of a week, and of a fortnight, after the receipt of the wound, we should not use any more serum, and we should probably get a more prolonged immunity than by giving the 1,500 units which some surgeons seem to prefer.”

As experience with the prophylactic employment of the antitoxin proceeded it became evident that there were cases which no amount of this agent would save, and these cases were those in which the wounds were not freed from foreign bodies and from devitalized tissue. These observations led to more thorough surgical treatment. Bruce wrote:

“The surgeon’s knife, after all is said and done, is the best means of preventing the occurrence of tetanus. It stands in the first rank as prophylactic. Dead putrefying tissue is the home, the favorite environment of the anaerobe. Place washed tetanus spores among healthy living tissues and there is nothing doing. Add a trace of gas-gangrene toxin, or a chemical irritant, such as saponin, or a physical irritant, such as earth or any foreign body, and the tetanus bacilli have their tails up at once. At the beginning of the war the treatment of wounds was not thorough enough at the primary operation. It was thought sufficient to wash out the wound and apply an antiseptic. Lately, however, the thorough excision of wounds has come more and more into vogue. * * * It has been made clear that many kinds of bacteria may lie latent in wounds for months or even years, and that complete healing of the wounds may take place in spite of their presence. These collections of bacteria lying in the depths or scar tissue, or sequestrum or bone, may give rise to no inconvenience, but, on the other hand, some slight accident such as a fall or a plastic operation undertaken months after the wound has healed, or even the ordinary operation of massage, may release them and start an attack of tetanus months or even years after the wound was received. Naturally it is the resistant spore-bearing anaerobic bacteria, such as tetanus and gas gangrene, which persist longest in the wounds; in fact, as Goadby has shown, end-sporers similar to tetanus bacilli have been found in bone sequestrum as late as three years after the infliction of the wound.”

In the beginning of the war much of the tetanus was attributed to the presence in the wounded tissue of *B. welchii* or the bacillus of gas gangrene. Bull and Pritchett, of the Rockefeller Institute of New York, prepared an antitoxin for this bacillus and experimentally demonstrated its value. By March, 1918, a double serum containing tetanus and the Welch bacillus antitoxin, was ready for use, and by July of the same year another antitoxin, that for the *Vibrio septique*, was prepared. This triple serum contained 1,500 units of tetanus, 250 units of gas gangrene, and 2,500 units *Vibrio septique* antitoxins. However, by this time the surgeon had learned to cleanse most wounds so thoroughly that during the remaining months of the war there was but little tetanus.

The value of the prophylactic administration of tetanus antitoxin was thoroughly demonstrated during the World War. Bazy reports on 200 wounded from the same sector. Of these, 100 received the antitoxin immediately after being wounded and only one developed the disease; in the remaining 100 who received no serum there were 18

cases. Columbino had under his care 200 wounded in the same battle. All but two had prophylactic injections. The two developed tetanus, while there was no case among the 198 who received the treatment. Walther had under charge 270 wounded German prisoners. To these he gave all the antitoxin he had. Among the treated there was only one case of the disease, while among the untreated there were 19. Fredet had in his ward many wounded French soldiers and 12 wounded German prisoners. To the French he administered antitoxin, but the German surgeon objected to the administration of a French preparation to his comrades. Of the 12 German wounded, six developed tetanus, while in a much larger number of the serum-treated French there was no case of the disease. Bruce says that before the prophylactic use of tetanus antitoxin in the British Army the incidence of tetanus per 1,000 wounded ran from 15 to 32, while after the adoption of prophylactic doses of antitoxin this figure fell to between two and three. Among the romantic incidents of the World War may be recalled the fact that tetanus prevailed among besieged British soldiers at Kut-el-Amara until an aviator arrived with a supply of antitoxin. As we have already stated, in our Civil War there were two cases of tetanus for every 1,000 wounded men; in the A. E. F. there were less than two per 10,000.

Repetition of the prophylactic dose every eight days proved to be of value. This is necessary because, as we have stated, whatever the dose administered, all the antitoxin has been eliminated within a week or ten days. It has been shown that tetanus spores may lie in wounded tissue quite indefinitely; and, furthermore, it sometimes happens that a wound is not infected at the time of its receipt, but becomes so later. The wounded man crawling over the ground may infect himself, or he may first receive the infection during transportation. There are cases known in which the infection has not entered the body through the wound inflicted, but through a bed-sore. It was certainly demonstrated during the war that no amount of antitoxin prophylactically administered will prevent the development of tetanus in all cases and, as Bruce has said, the surgeon is largely responsible and is the most important agent after all in the prevention of the development of this disease in war. That prophylactic injections do prolong the period of incubation, or, in other words, delay the development of the symptoms of the disease, has been abundantly demonstrated and, since the chance of recovery grows greater with increase in the period of incubation, it follows that even when the development of the disease is not prevented the mortality is lessened. Experience in the war has demonstrated that so long as the tetanus spores remain in the body the disease may develop. Sleeping tetanus spores in the tissue may be awakened weeks, months and even years, after they have been introduced. An operation for the removal of a foreign body should not be performed without the administration of

tetanus antitoxin. Starker has collected from the literature 18 cases of tetanus in which the disease developed more than 60 days after receipt of the wound, and in most of these the symptoms have first appeared after a secondary operation. In one instance the operation was for the purpose of removing a foreign body which had been embedded in the tissue for five and one-half years; six days later tetanus developed. In another, an operation for a traumatic hernia made 389 days later was followed after 12 days by tetanus. A fractured humerus was operated on four months later on account of nonconsolidation and after four days tetanus developed.

Cases of recurrent tetanus were occasionally seen during the war. Some of these followed manipulation of the wounded part, such as massage and passive movement. In other cases the recurrence of the symptoms after the lapse of days, and possibly weeks, could not be explained by any mechanical disturbance or irritation of the wounded parts. Sick reports a case in which the symptoms recurred five times within 15 months.

There are in the literature a few instances of chronic tetanus. Grober reports a case of a twelve-year-old boy who developed tetanus in consequence of a wound on a toe and was in a more or less constant spasm for two years, during which time he breathed only with the intercostal muscles and was nourished artificially.

The Value of Antitoxin in the Treatment of Tetanus.—The value of tetanus antitoxin as a curative agent has been made more evident by the experiences of the World War. In declared tetanus it often fails, but it gives better results than any other line of treatment and, in fact, is at present the only staff upon which we can depend. According to Mathieu, the mortality in 960 cases treated with serum has been 38.8 per cent, while in those not treated with serum it has been 80 per cent. According to Permin, the mortality among those receiving serum treatment was 57.7 per cent, while among those receiving no serum it was 78.9 per cent. While these results are not striking and leave much to be desired, they are sufficiently encouraging to justify the continuance of this treatment. Of course, if the wound is still an open one, excision may be undertaken; but, even when this can be done, it is desirable in declared tetanus to introduce into the body speedily as large an amount of the antitoxin as is possible. One has choice of subcutaneous, intravenous, intraspinal, and intraneural injections. It will probably be well not to rely exclusively upon any one of these procedures; indeed, all avenues may be used. The quickest way to reach every part of the body is by intravenous injection. An advantage is supposed to lie in the intraspinal method, since by this the antitoxin is brought into immediate contact with the cord in which the toxin is held in combination. The evidence has grown more convincing that, while the intraspinal

injection should not be the sole reliance, it should always be employed in connection with other avenues. Theoretically, intraneural injections are attractive. It is supposed that the antitoxin will follow the toxin and travel up either the axis cylinder or the neural lymphatic channels, but in declared tetanus it is evident that all motor nerves in the body are involved and it is quite out of the question to try to make an injection of antitoxin into every motor nerve. We are sure that the intraneural injection, whether employed or not, should not be the sole method. One hundred thousand units might be administered, subcutaneously or intravenously or divided between the two procedures, in the course of the first 24 hours. In employing the intraspinal method, a small quantity of the spinal fluid is withdrawn and replaced by from 3,000 to 10,000 units of the antitoxin. This may be repeated within 24 hours. Ashhurst reports two cases treated at the Episcopal Hospital in Philadelphia and compares the cost of the treatment. In the first, the patient received subcutaneously 99,000 units the first day, 65,000 the second, 60,000 the third, or a total of 224,000 units, which cost \$180; the other case received 3,000 units intraspinally on the first day, 750 units in the sciatic nerve and 750 units into the tissue around the wound on the second day. The patient recovered and the cost of the antitoxin was \$3. As a rule, it is well to get large quantities into the body, and this is most easily and satisfactorily accomplished by the intravenous route. In addition, the injection of from 5,000 to 10,000 units intraspinally is desirable, and this may be repeated daily. Park and Nicoll recommend the intraspinal administration as soon as possible of from 3,000 to 5,000 units and at the same time from 10,000 to 15,000 units both intravenously and subcutaneously. Andrewes increases the intraspinal dose to from 20,000 to 30,000 units, which is now possible since a highly concentrated antitoxin of 2,000 or more units per cubic centimeter has been obtained. Doyon suggests that patients receiving intraspinal injections should be kept with the head down and the body at an angle of forty-five degrees in order to aid the antitoxin in reaching the upper segments of the cord.

Bibliography

- ASHHURST, A. P. C.: *Arch. Surg.*, 1920, i, 407.
BINOT, J.: *Etude Experimentale sur le Tetanos*, Paris, 1899.
BROWNING, C. H.: *Hull's Surgery in War*, Sec. Ed., p. 103, London, 1918.
BRUCE, D.: *War Med.*, 1919, ii, 724.
BRUNNER, K.: *Jahresb. ü. d. Fortschr. a. d. Geb. d. Chir.*, 1917, xxi, 39.
COURMONT, J. AND DOYON, M.: *Le Tetanos*, Paris, 1899.
GUSSMANN, A.: *Beitr. z. klin. Chir.*, 1917, cvii, 326.
MENZER, M.: *Deutsch. med. Wehnschr.*, 1916, xlii, 218.
RANSOM, F.: *Lancet*, 1917, ii, 928.
SANFORD, A. H.: *Internat. Assn., Med. Museums*, 1918, Bulletin No. 7, p. 365.
STARKER, L.: *Arch. f. klin. Chir.*, 1918, cxi, 463.
TULLOCH, W. J.: *Jour. Hygiene*, 1920, xviii, 103.

CHAPTER XXVIII

VERRUGA PERUVIANA

Peruvian Wart; Carrion's Fever; Oroya Fever; Andean Wart

Description.—This disease is limited, so far as is known, to certain Andean valleys lying between the ninth and sixteenth parallels of south latitude and at elevations from 3,000 to 10,000 feet. Concerning these valleys Hirsch makes the following statement:

“All the localities affected by the disease have the same *natural features*. They are deep-cleft narrow valleys, whose sides are formed of bare rock (granite and diorite), and their bottom of clay covered with luxuriant vegetation and traversed by a mountain stream which may fall in cascades or flow smoothly. The disease occurs in these valleys just for so far as they continue to be narrow and gorge-like; wherever the valley widens, it may be not more than a few kilometers from the verruga-center, there is not a trace of the disease to be found. Owing to the conformation of these valleys, the day temperature in them is high (maximum of 95° to 103° F.) notwithstanding their elevation, whereas the nights are cold, so much so that a diurnal range of 25° to 35° F. is not infrequently observed. In contrast to the rainless coast of Peru, there is here a rainy season (August to November), although the rainfall is certainly not very copious; the dry season lasts from January to June, and in the transition months (December and July), violent storms blow from the Sierra. The population of the verruga-valleys belong mostly to the Ando-Peruvian race; they are very sparsely scattered, miserable in circumstances and degenerate in body. Their food consists of fruits, salted flesh, rice, a few esculent roots, and eggs; their drink is spring water, turbid from the admixture of mineral matters, which is fetched in earthen vessels and allowed to stand until the suspended substances subside.”

The best known endemic areas lie in the adjoining provinces of Ancachs and Lima. The disease does not occur along the coast and there is no endemic area at an elevation below 2,800 feet. The best studied area is that which lies along the railroad between Lima and Oroya. During the construction of this road in the early seventies of the nineteenth century the disease became epidemic not only among the navvies doing unskilled work, but also among the English engineers who had charge of the construction. Leaving Lima, this railroad follows the Rimac River, which, in the mountains breaks up into two tributaries, the Santa Eulalia and the Cocachacra, and it is along these and their tributaries that the deep gorges constituting the endemic areas of this disease are found. One of the tributaries of the Cocachacra is locally known as “aqua de verrugas” because of the belief of the natives that this disease is caused by drinking the water.

As we shall see later, there is still some difference of opinion as to whether what is now known as Oroya fever is a preliminary stage of

verruca or a distinct disease prevailing in the same localities simultaneously. Oroya fever varies considerably in the suddenness and intensity of attack. The onset may be gradual and accompanied by rheumatic pains, which may be confined to a single joint or muscle or be more widely distributed. The fever is intermittent and is accompanied by irregular chills which are followed by marked rise in temperature, often reaching 104° F. and even higher. Whether the onset be gradual or abrupt there is an enormous destruction of red-blood corpuscles, the number falling often within a few days from the normal of from four to five million per c.mm. to less than half that number. The blood picture is one of pernicious anemia. In all cases there is marked leucocytosis with great increase in the number of polymorphonuclears.

Usually, after the febrile stage, which has just been described, has continued for from a few weeks to some months, the skin begins to itch and the eruption occurs over the face, body or extremities. It may be more marked in one of these localities than in another. Sometimes the face and body practically escape, while all the extremities are thickly covered with the nodules. In some instances the eruption invades the mouth and involves the tongue, gums, palate, and fauces. At first the cutaneous eruption consists of erythematous spots with small vesicles which rarely become pustular. These are soon supplanted by nodules, which vary greatly in size. They look like warts, become fungous, and bleed readily. Castellani and Chalmers make the following statement concerning the eruptive stage of this disease:

“The area of the skin on which the spots appear is usually edematous, a feature most commonly observed on the legs. With the appearance of the eruption the fever declines, the general symptoms abate, and the patient feels better, but the blood shows a marked diminution in the red cells, some of which are nucleated, and a corresponding reduction in the hemoglobin, and this anemia may be aggravated by hemorrhages from the nodules, which may be so severe as to cause the death of the patient. This blood condition has been carefully investigated by Monge, who finds that at the commencement of the illness there is oligocythemia, microcytes, macrocytes, normoblasts, and megaloblasts (under 1,000 per cubic millimeter), with poikilocytosis, polychromatophilia, and granular red cells. The hemoglobin value is raised. The white cells are increased, and there is slight polymorphonucleosis. The mononuclears have well marked basophilic protoplasm. At this stage the verrugas may develop in the internal organs, and cause serious symptoms; thus in the larynx they will cause dyspnea; in the bronchi, bronchitis; in the lungs, pneumonia; in the pleura, pleurisy; in the nose, epistaxis and difficulty in nasal breathing; in the esophagus, dysphagia; in the intestines, bloody diarrhea; in the meninges, brain symptoms; in the eye, amblyopia; and in the uterus, metrorrhagia.”

In cases ending in recovery successive crops of these warty growths may come and go for six months or longer and finally disappear. The ulcerating nodules gradually cease to discharge any secretion and cicatrize. It may be well to repeat that the febrile stage, which we have

described as preliminary to the eruptive stage of verruga, is believed by some, especially by Strong and his collaborators, to be a disease wholly distinct from verruga. The febrile stage, whether it be a distinct disease or preliminary to the eruptive stage is easily recognized in endemic areas by the rapidity with which the red-blood corpuscles are destroyed and the blood picture of pernicious anemia is developed.

History.—While the conquest of Peru was still in progress, Zarate, Chancellor of the newly-founded City of Lima, wrote as follows:

“This country, situated between the tropic and the equator, is very unhealthful; the men here suffer from a wart or small tumor like a boil, very malignant and dangerous, which appears on the face or other parts of the body, and is more destructive than the smallpox and almost as disastrous as the plague itself.”

Other historians of that time tell us that numbers of Pizarro's small army died from hemorrhages resulting from gangrenous ulcers on the skin. One narrator says that one-fourth of Pizarro's seven hundred men died from this cause. At first, it seems rather strange that from the middle of the sixteenth to the middle of the nineteenth century nothing was heard of this very striking and peculiar Andean disease. A brief statement, however, of the topographical divisions of this country, with their marked differences in climate, flora, and fauna, including races of men with different habits of life and widely variable stages of civilization which, from time to time under political domination, fluctuated markedly, will do much, in our opinion, to explain the absence of any account of this disease through this long period. The Andean region, including the whole of Peru and extending farther, both north and south, is topographically, geologically, and climatically divided into three distinct areas. The maritime portion bordering on the Pacific and extending eastward to the Andean foothills is a sandy plain of variable width, traversed at variable intervals by two kinds of rivers flowing into the Pacific. Some of these rivers rise in the higher mountains, are fed from the snow-capped peaks, and flow throughout the year, while others have their source in the lower elevations and their beds are dry at certain seasons. It will be seen from this that necessarily the littoral varies greatly throughout its length north and south, in its fertility and its ability under natural conditions to support a population. So far as we can learn, the Pacific border of South America in pre-Columbian days was inhabited but sparsely and with an inferior race of people. The disease which we are discussing is not now, and never has been, indigenous to this region. The second transverse area of the Andean territory is known as the Sierra and consists of a region of varying width and at altitudes running from 3,000 to 12,000 feet. The civilization of the Incas was confined to the Sierra and this presents a great variety not only in altitude, but in temperature and

fertility. The third division of the western part of South America has always been known as the Montañas. This occupies the eastern slopes of the Andes extending into the jungles and swamps of the upper Amazon and its tributaries. With this division we are not concerned in our present study; in fact, our present interests confine us to the Sierras. Here existed the ancient civilization of Peru. It was in this region that the Spanish invaders found a people or peoples possessed of an unexpected civilization and owners of great wealth. The conquerers did not take up their residence in the Sierra area, but withdrew and began building Spanish cities along the coast in the maritime area. From 1530 or thereabouts, for nearly 300 years the viceroys of Spain occupied the Peruvian coast, held in slavery and worked in the mines the descendants of the Inca tribes and took no further interest in the Sierra region than to draw from it wealth secured by the toil of its native inhabitants; in other words, during these 300 years there was no human interest, or but little, in the country which produced the ancient civilization and in the gorges of which the disease we are now studying, existed before the Spanish conquest, has continued since that time, and has only recently attracted attention.

One of the earliest modern writers on *verruca peruviana* was Smith, who spent some years in Peru, and wrote a most valuable series of papers on the disease in the three areas we have mentioned. In discussing the diseases seen in the Sierras, he makes the following statement:

“By verrugas is meant a disease which is introduced by more or less pyrexia, and several days or perhaps weeks of aching pains of the body and limbs more especially; and these precursory symptoms are relieved by an eruption of delicate wart-like excrescences of vascular papillae, very tender and apt to bleed freely when roughly touched. The patient, therefore, is generally unable to walk when the eruption is copious; because the motion of the body in the early stage of it would occasion troublesome hemorrhage, and even when lying in bed, the sheets are usually stained with blood and lymph. The crop is sometimes scanty and confined to the extremities; but on other occasions, it breaks out on the face and body as well as on the extremities. The eruption, which is often as close as confluent smallpox, is successive; one crop coming on as another drops off, and lasting perhaps for six or eight months, or more. Here and there I have observed some of these papillae or warty excrescences attain the size of a raspberry, whilst others on the same individual were not larger, and some even much less, than common red currants, or trout's spawn, which they somewhat resemble when only covered with a very thin pellicle on their summit. On being cut at the root by ligature, I did not find the hemorrhage profuse; but observed that they grew again with great rapidity, and even seemed to attain a larger size, whilst they certainly became more irritable by this treatment. To cauterize them will be found to have no better result; but when allowed to run their natural course they gradually crust, fade, and drop away. This disease, which appears to be an indigenous variety of yaws, is not confined to any particular race or complexion of people nor generally believed to be contagious or infectious, though some suspect it, without sufficient reason, to be an-

alogous to syphilis. It is properly a disease of the warm glens; and all the cases which I saw in Lima occurred in individuals of white race who had caught the disease in some quebrada of the Sierra, or in the cabezadas or head-lands of the maritime valleys."

In 1845 Tschudi wrote on this disease, giving its symptomatology, and discussing its etiology. He says that along the trails leading from the ocean to the Cordilleras there are many springs where the mule drivers permit their animals to satisfy their thirst but themselves decline to drink, saying "es agua de verruga." He mentions certain villages in the valley of the Cocachaera where the disease was at that time, and continues to be, endemic. He says that Peruvian wart is never known to occur below an altitude of 2,000 meters or above one of 5,000. This author expresses no definite opinion concerning the causative agent in this disease, but he is inclined to attribute it to the effects of the cold air on an overheated body, possibly intensified by the drinking of large quantities of cold water.

Smith first went to Corro de Pasco, a mining town at an altitude of about 14,000 feet, in 1826. He states that this is probably the highest inhabited town of from five or six to fifteen or sixteen thousand souls upon the face of the earth. Even at that time adventurers from various parts of Europe and America were coming to this city in their hunt for hidden treasures. Speaking of the change in living conditions, Smith in 1858 wrote as follows:

"The dreariness and discomfort of the wet season in this climate can hardly be conceived by those who did not visit it as it was under the Spaniards. But now, the comforts of coal fires, chimneys, and glass windows, introduced by the English mining company have become general and rendered this naturally inclement region of the Andes a paradise compared to what it was at the close of the War of Independence."

It might be added that, so far as we can ascertain, the improvement in living conditions as described by Smith, has not in any way curtailed the prevalence of the disease now under consideration. In the fifties of the last century, Salazar, Oriosola, and other Peruvian physicians wrote extensively on verruga, but devoted themselves largely to symptomatology, pathology, and treatment. They added nothing to our knowledge of the etiology of the disease.

In 1871 Dounon, a French naval surgeon, after visiting the endemic villages in the valleys of the Cocachaera, wrote a description of the disease, which was the most complete statement made up to that time. He convinced himself by drinking suspected waters and by permitting his assistants to do the same thing that the source of the disease was not in the water. He reported that certain domestic animals—dogs, cats, and fowl are subject to the disease and present characteristic eruptions on their bodies. In the quadrupeds, growths were found fre-

quently to have pedicles and to stand out like mushrooms. This form is seen sometimes on man. Dounon concluded that the disease is not contagious. He observed that while large families sometimes occupied the same bed, the disease was not transmitted from the infected to the uninfected. In the General Hospital at Lima, patients with this disease were kept in the general wards where they came into contact not only with the physicians, but with other patients and nurses and there had never been observed a case of infection acquired under these conditions.

Following Dounon's publication, great enthusiasm began to be displayed in the study of this disease and, unfortunately, this zeal caused the death of a medical student in the University of Lima, Carrion by name, who, on August 27, 1885, injected into both his arms blood taken from a verruga nodule. Twenty-one days later he developed a fever from which he died on October 5. This sacrifice, however, did not settle the question of the transmissibility of verruga. There is no proof that this self martyr developed verruga or that this disease had anything to do with his death. It did lead, however, to a discussion which had previously arisen as to whether the fever which often precedes the eruption is a part of the eruptive disease, a prodromal stage, or a disease *sui generis* and with no causal relation to verruga. Since this unfortunate accident Peruvian physicians have designated the acute fever which is prevalent in the same endemic areas as verruga and which precedes or accompanies the eruptive disease so frequently, as Carrion's disease or fever. Bacteriologic investigations were begun and claimants of the discovery of the causal agent of both the fever and the eruptive disease frequently appeared. Bacilli and micrococci were found, isolated, and used in inoculating animals, with results which in some cases at least, satisfied their discoverers that they had found the true virus; but none of these satisfied other investigators.

In 1898 Odriozola published in French a most exhaustive monograph on Carrion's disease and verruga peruviana. In 1901 Barton, of Lima, found a microorganism in the blood in Carrion's disease. At first this investigator was inclined to the opinion that the organism which he found was a bacterium and he stated that it resembles bacillus coli communis but is not identical with this well-known organism. The study of this parasite was continued by Barton and others, opinion being divided as to whether it is a bacillus or a protozoan. Some investigators believed it to be *B. paratyphosus* B, while others were inclined to the opinion that it is best classified as a member of the Gärtner group. Most of these investigators found this organism only in the febrile state or in what is known as Oroya fever or Carrion's disease and did not find it in the eruptive stage or in verruga. They, therefore, concluded

that Carrion's disease and verruga are two distinct diseases prevalent in the same localities and found frequently, either in sequence or simultaneously, in the same individual.

In 1915 the Harvard School of Tropical Medicine sent an expedition, consisting of Strong, Tyzzer, Brues, Sellards, and Gastiaburu, to Peru, especially commissioned to study Oroya fever and verruga peruviana. The report of this Commission contains the following statement:

"According to the generally accepted opinion among the physicians of Peru at the time of our arrival in Lima, the disease verruga peruviana in the severe form begins with an initial stage known as the *fièvre grave de Carrion* which is characterized by a fever which lasts from 15 to 30 days, profound anemia, prostration, and a high mortality. If the patient does not die in this stage the fever begins to abate, and the eruptive, or verruga stage commences. If the eruption is generalized and abundant, then it is stated that the patient is sure to recover. In the chronic or mild form of the disease, which is said to comprise the great proportion of the cases, there is moderate fever of intermittent or remittent character, and pains in the joints are common; more or less anemia is present. The eruption is said to be the culminating feature in both forms, and it appears under various types which, according to the special characteristics they reveal, are termed 'miliary,' 'nodular,' or 'mulaire.'

"After studying these conditions in Peru, we concluded that verruga peruviana and Oroya fever are two distinct diseases. We have been able to show that the former is due to a virus which may be transmitted to animals by direct inoculation and which produces definite lesions in them, and that the latter is due to an organism parasitic in the red-blood corpuscles and endothelial cells, and sufficiently distinct from the other hematozoa to be placed in a new genus. So far this organism has not been successfully transmitted to the lower animals. The parasite which we consider to be the cause of Oroya fever produces in man fever, and in severe infections a rapid and very pernicious form of anemia, which results in extreme prostration and frequently in death. Verruga peruviana, however, is evidently very rarely a fatal disease when uncomplicated with other infections. It is particularly characterized by an eruption upon the skin which may assume a very different appearance in different stages of the disease."

The Virus of Oroya Fever.—Strong and his collaborators state that, while Oroya fever and verruga peruviana have in general the same geographical distribution, the endemic areas are not necessarily the same, although this point has not been worked out with desirable detail. The virus of Oroya fever is the organism first seen and described by Barton. It occurs in the red-blood cells and morphologically exists in two forms—a rod-like body from 1.5 to 2.5 microns in length and from .2 to .5 micron in thickness; a spherical or rounded body from .5 to 1 micron in diameter. It may be stained by the Giemsa method in either fresh smears or fixed preparations. Not being able to determine the classification of this organism, Strong and his collaborators propose that it be designated, for the present at least, as *Bartonella bacilliformis*. It has not been grown in artificial cultures nor has any one succeeded in inoculating animals with it. Mosquitoes were permitted to bite severe cases of Oroya fever, and subsequent search in these

insects for the organism was made but no evidence of the presence of the parasite could be discovered in the stomach or salivary glands of the insect.

The Virus of Verruga Peruviana.—Although Strong and his collaborators were unable to find any organism to which they could attribute this disease, they did succeed in inoculating a certain percentage of the monkeys upon which they experimented, with matter taken from the cutaneous eruptions. Of their successes in inoculating monkeys, they wrote as follows:

“If the skin over the eye is scarified and a small portion of verruga nodule rubbed into the abrasions, after an incubation period usually of ten to twenty days, small papules appear which gradually enlarge and later assume the typical picture of the verruga nodules as seen in human beings. The nodules thus produced also have a similar histological structure to those observed in man, a fact that will be referred to again. We have transmitted this virus from animal to animal through 12 successive series of monkeys since our departure from South America over a year ago. In 34 monkeys typical lesions have been produced in this manner. When the monkey is inoculated with the virus either directly from man or from another monkey, no generalized eruption occurs; as in the case when this animal is inoculated with smallpox virus, only a modified form of the disease develops. It is probable that the monkey is not as susceptible to the virus of verruga or even to that of smallpox as is man. The virus of verruga also calls forth no appreciable febrile reaction in the monkey inoculated with it, and none of the monkeys died from the inoculation with this virus. The lesion in the monkey usually begins to regress four or five weeks from the time of inoculation.”

Experiments were made for the purpose of determining the filtrability of this virus, but the results were not satisfactory. Strong and his collaborators discuss the possibility of vaccination as a means of protection against verruga. In this connection they make the following statement:

“In Peru the popular opinion prevails that one attack of verruga peruviana confers immunity against subsequent attacks. It is certainly exceptional to find individuals who have suffered two distinct attacks of the disease. We have performed experiments in animals with the idea of discovering whether immunity resulted after inoculation of the verruga virus. We have called attention to the fact elsewhere in this report, that when the monkey is inoculated with the virus either directly from man or from another monkey, no generalized eruption occurs, but just as in the case when the calf is inoculated with smallpox virus, only a localized lesion develops. We have found that monkeys may be very successfully immunized by a single cutaneous inoculation of the verruga virus, and when such monkeys, are reinoculated no lesion develops. In all instances in which the monkey is successfully vaccinated with the virus in this manner, it has been protected against a second attempt at infection. By successful vaccination we imply the development of the local lesion following the inoculation. Animals have been found to be immune for as long a period as six months after the primary inoculation. It therefore seems probable that by using the virus after several passages through monkeys, that man may also be successfully vaccinated against this disease in a similar manner to that which is employed against smallpox. The virus

of verruga, however, so far has not been successfully glycerinized, as we have called attention to elsewhere. This method of vaccination against verruga seems favorable, since in one human case that was inoculated with the virus only localized lesions developed. It is hoped that in the near future vaccination may be given a careful trial in Peru where the disease is so prevalent."

Transmission.—Whether verruga peruviana and Oroya fever are different stages of the same disease or are two distinct diseases without any direct relationship, the agent of transmission of the virus or viruses, is not known. Townsend, who for many years has been connected with the Entomological Department of the Peruvian Government, is strongly of the opinion that the vector is a species of phlebotomus, to which he has given the name *P. verrucarum*. This little fly, theoretically at least, fills the bill when we study its nature and habits. Many observers tell us that if one spends a night in an endemic area he may acquire the infection. The traveler may pass through in the daytime with impunity, but if he lingers overnight in a valley in which this disease is, or these diseases are, prevalent, he may subsequently give evidence of his infection. The phlebotomus is a minute blood-sucking nocturnal fly which is able to pass through ordinary mosquito netting. After impregnation, the female seeks some animal and fills herself with blood. She then retires to some damp place, usually a minute crack in a stone or brick, and deposits her eggs, which number from 20 to 80. Usually from four to six days, depending upon the temperature, are required before the eggs hatch. The larvae, which are only from two to five millimeters in length and which are not easily detected since in color they resemble the stone upon which they are deposited, develop into the pupal stage, the duration of which is from eight to thirty days. Castellani and Chalmers describe the habits of the phlebotomus, as follows:

"These little flies are essentially nocturnal in their habits, but are attracted by light. During the day they lie up in cool shady places in houses, etc., under bricks, in hollow trees, behind shutters, books, pictures, etc., often in bathrooms and more often in latrines. They are very small, and can easily pass through the meshes of ordinary mosquito curtain and fill themselves with human blood; or, failing this, they will content themselves with animal blood—e. g., that of cattle, dogs, frogs, geckos, serpents, lizards, etc. They fly quite silently, and only the female bites, and that only at night. She appears to be stimulated in her biting propensities by an increase of humidity and temperature, and will even crawl under the bedclothes to get at her victim. During the act of biting the posterior end of the abdomen is raised, while the whole abdomen becomes much distended with blood and reddish in color, except at the posterior tip. * * * The larvae are very difficult to find, because they are so small, while the pupae are even more difficult to see, because not merely are they small, but they are also of a color similar to the stones to which they are attached. Hence the habits of larvae and pupae are not well known, and require to be restudied. Their presence may be determined, even when they cannot be found, by placing the stones in a glass

case, or under a fine netting, when the adult flies will appear in due course if any pupae are present.”

Prophylaxis.—Until we know the vector in this disease, or these diseases, it will be necessary to speak in a very tentative way about protective measures. From what has been said, it is quite evident that no one acquires the disease outside of the endemic areas, and that even in these there is no danger of infection during the daytime. It has been suggested that whatever the insect engaged in transmission may be, it avoids lights and keeps out of strong air currents. When, therefore, one is compelled to spend a night in an endemic locality, artificial light and fans may be employed. Both of these, however, may be difficult to secure in such out of the way places as the Andean gorges. As a protection against the phlebotomus, Crawford recommends an ointment consisting of one drachm each of oil of anise and oil of eucalyptus; one-half drachm of oil of turpentine, and one ounce of boric acid ointment. It is said by Giana that when the mortality from Oroya fever became an important matter in the construction of a railroad through an endemic area, a day's work was completed and the workmen left the locality before sunset and the prevalence of the disease was greatly reduced.

Bibliography

- DOUNON, P. V.: Arch. de Med. Navale, October, 1871, p. 255; Etude sur la Verruga, Maladie Endemique dans les Andes Peruviennes, Paris, 1871.
MONGE: Jour. London School Tropical Med., 1912.
ODRIOZOLA, E.: La Maladie de Carrion, Paris, 1898.
ORIOSOLA: Med. Times & Gaz., September, 1858, p. 280.
SMITH, A.: Edinburgh Med. & Surg. Jour., July, 1842, p. 59; 1858, p. 67.
STRONG, and Collaborators: Report of the First Expedition to South America of the Harvard Medical School, 1915.
TOWNSEND: Am. Jour. Trop. Dis., 1915, iii, 16.
TSCHUDI, J. J.: Arch. f. Physiol. Heilkunde, 1845, iv, 378.
ZARATE, A.: Conquest of Peru, 1543. (English translation).

CHAPTER XXIX

ROCKY MOUNTAIN SPOTTED FEVER

Black Fever; Blue Disease

Description.—This is a specific infectious disease which follows the bite of a certain tick, *Dermacentor andersoni*, whose habitat lies in certain valleys in the Rocky Mountains. The virus of this disease has not been fully and satisfactorily identified. During a period usually of from two to eight days following the bite, the only symptoms recognized consist of pains radiating from the place of puncture. The period of incubation terminates suddenly in a chill, which may recur at irregular intervals, though, as a rule, with decreasing severity, throughout the course of the disease. The initial chill is accompanied by headache, pain in the back, joints, muscles and bones, with bronchial cough. Following the initial chill, fever develops rapidly and may on the second day reach 104° F. and from the fifth to the seventh day in severe cases may register from 105° to 107°. There may be an evening exacerbation and a morning fall, with step-like increase from day to day as occurs in typhoid fever. The average duration of the fever is about two weeks, though the temperature may not permanently fall to normal within less than four weeks. In cases of recovery the fever disappears by lysis and in fatal cases the temperature may fall several degrees below normal before death.

The pulse, as a rule, keeps somewhat ahead of the proportion indicated by the fever. In severe and fatal cases it may reach 150 per minute and even higher. The blood is generally darker than normal, is somewhat less fluid, and the hemoglobin content usually shows a decrease during the progress of the disease. In severe cases, the low muttering delirium, so frequent in typhoid fever, is in evidence and is accompanied by picking at the bedclothes and other purposeless movements.

The characteristic eruption appears from the second to the fifth day after the chill, sometimes later. It is first seen about the wrists and ankles or on the back, gradually extending however to the entire body, the abdomen being about the last part reached. It may cover the palms of the hands, the soles of the feet, and the scalp. At first one sees rose-colored macules, generally in circles, varying in diameter from 1 to 5 mm. The color becomes, as the disease progresses, bluish and purple, thus giving to the disease some of the local names by which it is designated. In severe cases the eruption becomes confluent, leaving only brownish spots uncovered and presenting an appearance which has been likened to that of a

turkey's egg. There may be edema of the face and extremities. About the third week of the fever, desquamation begins and may persist for days after the patient is quite recovered. In severe cases there may be cutaneous gangrene, especially on the elbows, fingers, toes, and scrotum. The mortality varies so widely in different localities that it suggests the action of different strains of the virus. In the Bitter Root Valley of Montana the mortality has been seventy per cent or over, while in Idaho, Nevada, and Wyoming the fatality is much less and may be not more than three per cent. It is believed by local practitioners and by those who have visited the region and studied cases in their homes that there are mild types of the disease, even in those regions where the mortality is greatest. The most constant postmortem finding is enlargement of the spleen, with softening of the tissue of this organ. One attack confers immunity in both man and animals. The transmission of the disease from man to man by the bite of the tick was demonstrated by McCalla and Breerton.

History.—Physicians along the Snake River in Idaho state that this disease has been known in that region since 1873, but the first published account which we have been able to find is that of Maxey, of Boise, Idaho, who defined the disease as follows:

“An acute endemic, noncontagious, but probably infectious febrile disease, characterized clinically by a continuous moderately high fever, severe arthritic and muscular pains, and a profuse petechial, or puerperal eruption in the skin, appearing first on the ankles, wrists and forehead, but rapidly spreading to all parts of the body.”

In 1902 the State Board of Health of Montana requested Wilson and Chowning to make a study of the disease in the Bitter Root Valley. These investigators made a stay of some weeks in the infested region in May and June of 1902 and repeated their visit one year later. While engaged in this work they were visited and assisted by Anderson and Cobb, of the U. S. Public Health Service, and by Wesbrook, of the University of Minnesota. Their investigations were confined to the Bitter Root Valley, which is bordered on the west by the Bitter Root Mountains and on the east by the Granite Mountains. Through this valley flows the Bitter Root River for a distance of quite 50 miles, receiving tributaries on both sides. The disease is confined to that part of the valley which lies west of the Bitter Root River and which varies in width from five to ten miles. Up to that time (1903) over 200 cases of a severe type, with a mortality of from seventy to eighty per cent had been reported in this narrow strip west of the Bitter Root River, while only seven cases had been known in the more extensive part of the valley lying to the east of the river and it was shown that at least some of these had acquired the disease on the west side of the river. The disease was found to occur chiefly in the spring, the earliest known case occurring on March 17 and the last for the season on July 20, while most of them occurred between May 15 and June 15. Con-

cerning the topography and climate of this narrow strip of land, Wilson and Chowning make the following statement:

"The Bitter Root range of mountains is very rugged, the top being covered with snow until about July 1. The range on the east side of the valley is less rugged, though the snow remains almost as long in spring as on the west side. On the foothills the snow melts from sunny exposures as early as February, the bulk of it disappearing in April and May. The climate of the valley is very mild, as is evidenced by the many orchards of apple, pear, cherry and plum trees. The altitude of the valley is about 3,500 feet above sea level. The population is made up largely of fairly well to do ranchers, the majority of whom have come from Missouri, Georgia and the Carolinas. They are, as a rule, cleanly and healthy. The lumber industry is an important one, and many cases of 'spotted fever' have arisen about sawmills and on ground recently cleared of timber."

Wilson and Chowning had no difficulty in incriminating a tick, which was submitted to Stiles, of the U. S. Public Health Service, for identification, who finding reasons for considering it a new species, designated it as *Dermacentor andersoni*. It was found that this tick puts in an appearance in sunny spots as soon as the snow leaves the ground bare, which is usually about the middle of February. The tick, however, remains inactive during the greater part of March and becomes most numerous during May and June. About the middle of June it is seen less frequently and disappears about the middle of July.

Wilson and Chowning convinced themselves that the virus of the disease is a hematozoon belonging to the *Piroplasma*; they named it *Piroplasma hominis*, and suggested that the disease be known as "piroplasmosis hominis." So far as the tick is concerned, the work of these investigators holds, but others have not been able to confirm the existence of the organism which they describe.

In 1906 Ricketts began his studies which have greatly advanced the solution of the problems connected with this disease. He demonstrated that the monkey (*Macacus rhesus*) and the guinea pig are highly susceptible to the virus of this disease; that in these animals the incubation period is approximately the same as in man; that the course of the fever, the eruption, and the anatomic changes correspond closely with these features in man; that indefinite transmission from animal to animal is possible even up to 100 generations; that the cell-free serum of infected blood contains large amounts of the virus; that the virus is present in abundance in artificially induced leucocytic exudates free from red blood cells; that prolonged centrifugalization of serum does not free the overlying parts from the virus; that it is impossible to free the blood cells from the virus in defibrinated blood by ten or twelve washings with physiologic salt solution, though this process decreases the virulence of the blood.

Commenting upon the last-mentioned demonstration, Ricketts wrote:

"It was hoped that experiments of this nature might bring out evidence in favor of

or against the piroplasma theory of Wilson and Chowning. I believe, however, that the results do not justify positive conclusions for or against this theory. In the experiments cited above the cell-free serum proved rather highly infective; this event, however, does not preclude the possibility of a piroplasmatic infection, for, although piroplasmas invade the erythrocytes extensively in all known piroplasmic diseases, it is self-evident that the plasma must be the medium through which the organisms reach the erythrocytes. Hence in all piroplasmoses there must be many extracellular organisms at some stage of the disease."

Ricketts further demonstrated that the virus does not pass through a Berkefeld filter; that one attack of spotted fever renders an animal resistant to further attempts at inoculation, and in this respect the experimental disease in animals resembles the natural disease in man; that an immune serum can be obtained and its value demonstrated by its protecting guinea pigs against 20 or more minimum pathogenic doses of the diseased blood; that the offspring of immune female guinea pigs also are immune for a period; that the disease may be transmitted to monkeys and guinea pigs by infected ticks as well as by blood injections; that both male and female ticks may transmit the infection; that the disease may be acquired and transmitted by the larva, the nymph, and the adult male and female, that is to say, by the tick during any of its active stages; that the association of the virus with the tick is intimate, as is shown by the long duration of infectivity in the tick, the retention of infectivity during molting, and the hereditary transmission of the virus; that there is no reason for suspecting that the tick suffers from the virus as it proliferates in its body; that in the infested area only a small proportion of the ticks are infected.

This disease may be induced in guinea pigs by the injection of infected blood or pulverized infected ticks at any stage of development, including their eggs, or by the bite of infected ticks. Following such inoculation there is an incubation period of from two to five days, interrupted by a sudden rise in temperature, which may measure as high as 105° to 106° , and which continues without remission for a period of from six to twelve days or until the death of the animal from four to twelve days after its onset. In males the scrotum, and in females the vulva, is swollen, and in exceptional cases, hemorrhagic. The spleen is enlarged and cyanotic in color. Many of the lymph glands are congested, swollen, and occasionally hemorrhagic. If white guinea pigs be shaved there may be seen some hours or days after the onset of the fever, a generalized rose-colored eruption, which is most marked on the back and extremities. When recovery results, the animal is immune to as much as 1,000 doses of infected blood. Transmission from animal to animal by infected ticks is easy. All that is necessary is to permit one or more uninfected ticks to feed for several hours on an infected guinea pig and then transfer the insect to a healthy

animal. The tick takes its own time in feeding and unless it be very hungry when placed on a fresh animal, it may refrain from feeding for some hours. It appears from the work of Ricketts that when a tick feeds upon an infected animal it may immediately afterwards be proved to be infectious when fed upon an uninfected animal or when its body is crushed and a suspension injected into the animal. Apparently, however, some time must elapse before a generalized invasion of the tick is accomplished. That this stage is finally reached is shown by the fact that every part of the tick, including its eggs, bears the infection. When a tick becomes infected the virus reaches every part of its anatomy, leaves the body in the eggs, and continues existence throughout the larval, nymphal, and adult life of the next generation. Furthermore, Ricketts took larvae from uninfected female ticks, fed them on infected guinea pigs, and after these larvae had become nymphae, they were placed on clean guinea pigs, which they infected. In like manner it was shown that the nymphae may both receive and transmit the virus, and, having received it, it continues with them in adult life.

In 1909 Ricketts made the following statement:

"A polar staining bacillus is found in the eggs of infected ticks, and also in their ovaries, alimentary sacs and salivary glands. It exists frequently as a diplobacillus in all these localities. A similar organism is found in the blood of infected guinea pigs, lying in the plasma and not infrequently in nucleated blood cells. It is seen also in the blood of infected men. In the blood it is usually seen as a bacillus or diplobacillus or as a diplococcoid form, the latter perhaps being a small bipolar organism. In size it approximates that of the influenza bacillus, probably being a little smaller. A specific relationship to spotted fever is indicated by its great susceptibility to agglutination by the serums of animals and of man which have recovered from spotted fever. Dilutions of 1-320 and of 1-400 cause complete agglutination with some serums, and so far no serum has been tested which did not agglutinate strongly in a dilution of 1-320. Normal serums from the guinea pig agglutinate moderately in a dilution of 1-2 and sometimes weakly in a dilution of 1-20, but not higher. The normal serum of man agglutinates to a similar degree. An emulsion of crushed infected eggs serves as a source for the bacilli in the agglutination tests. The facts cited are strong evidence that the microorganism described is the cause of spotted fever. It is, of course, desirable that all possible evidence bearing on the relation of the bacillus to the disease be accumulated, and the subject is being studied further for this purpose."

The death of Ricketts from typhus fever acquired during experimental work on this disease in Mexico, was a great loss to progressive medicine. In this connection, it is proper to state that McClintie, of the U. S. Public Health Service, in 1911, while inoculating animals with the virus of Rocky Mountain spotted fever, contracted the disease and died.

Wolbach (1916-1919) has continued the study of the virus of Rocky Mountain spotted fever and the morphologic elements which he describes are most probably identical with those discovered by Ricketts. Wolbach finds these organisms generally distributed in infected ticks and guinea

pigs. They are especially abundant in endothelial cells and the lesion which results from their activity is proliferative in character. Similar bodies have been found in trench fever and in typhus fever. Rocha Lima has given to these organisms the name of "Rickettsia," and this term has been generally adopted. There is still some discussion concerning the nature of rickettsia bodies and their relation to the diseases in which they have been reported. Some hold that rickettsia bodies are not living organisms, but consist of granules of precipitated albuminous substances. Some claim to have found them in lice and ticks which have never fed on infected men or animals. Others still claim that the viruses of these diseases—Rocky Mountain spotted fever, typhus fever, and trench fever, are filtrable, and if this be true the rickettsia cannot be the causal agents of these diseases. This work has been recently reviewed by Arkwright, Bacot and Duncan, whose conclusions are in favor of the rickettsia as being living pathogenic organisms.

The Habits of the Tick.—Paine gives the following description of the life-cycle of the tick:

"There are four stages of the tick. The egg, the larva, nymph and adult stages. The larvae and nymphs live upon small rodent animals (ground-, rock-, and pine-squirrels, woodchucks, chipmunks, weasels, gophers and badgers). These smaller animals are too agile to permit the adult ticks to remain upon them, so the full-grown wood ticks select as hosts the sheep, horses, cattle, mountain goats, bear, coyotes, and elk. Beginning with the adult tick and following the different stages of the tick we can trace its life-cycle; both the adult male and female ticks live upon sheep, horses, and cattle, etc. They may both be found upon the same animal. The male buries its head in the host, feeds a while, releases itself, then crawls around looking for the female, and, if the latter be found (probably attached and feeding itself), the male attaches just below the female and copulation takes place, after which the male—upon becoming engorged with the blood of the animal upon which it is—falls off and dies. The female requires more time for engorgement and remains for a longer time; when engorged, she releases herself, falls off, wherever that may happen to be—in the sage bush, wheat grass, or upon the rocks—oviposits her eggs and then dies. If male and female ticks do not mate, the eggs laid by the female do not hatch out, as they are not fertilized. If adult ticks do not find a host upon which to engorge they can probably live through two seasons and, if no host be then found, they die. If copulation has occurred, the *eggs* develop into larvae within two weeks; if a small rodent animal be found as a host, the *larvae* attach themselves, engorge, fall off, molt within two weeks and become nymphs. If no host for the larvae be found, they probably die at once from starvation. The *nymphs* lie dormant till the following spring (because they don't become nymphs until August and by this time the small animals acting as hosts have gone into winter quarters, have hibernated). The following spring the nymphs search for a host, and if one be found they attach themselves, engorge in a week, fall off, molt within two weeks and develop into adult ticks. The above time limits are for the most favorable circumstances. These adult ticks by some instinct or other do not attach to an animal. (Nature seems to tell them if they attach and engorge that year their eggs will not develop, because if the eggs are hatched out in August the larvae would find no host and would quickly die.) If the nymphs do not find a small animal upon which to

nourish themselves the first spring, they can probably live through two seasons, and, if a host be found, they will attach, engorge and continue the cycle."

There are several species of the tick. According to McClintic, that found in Wyoming is *D. modestus*.

Geographical Distribution.—Up to the present time (1922) Rocky Mountain spotted fever has been found in the following states: Idaho, Montana, Nevada, Oregon, Wyoming, Washington, California, Colorado, Utah, and South Dakota. It will be understood that even in these states the disease is not widely distributed but is confined to certain localities. At the time that Wilson and Chowning made their studies (1903) the disease had been found in Montana in only three localities,—the Bitter Root Valley; a small valley near Bridger about 250 miles east and 75 miles south of Bitter Root Valley, and a narrow canyon on Rock Creek about 20 miles east of the Bitter Root Valley.

In 1915 Fricks found Rocky Mountain spotted fever quite liberally scattered throughout southeastern Montana, especially about Miles City. A former survey of this region had failed to detect ticks and their introduction and spread are believed to have been sudden. As is well known, Miles City has been for years a large horse market. These animals are gathered in from every part of the Northwest and most of them are sold for distant transportation. Sales are held monthly, and during the World War thousands of these horses were sent to Europe. It frequently happens, however, that on account of certain animals not being up to par they are sold to local stockmen at Miles City and consequently are more or less scattered throughout the surrounding country. Theoretically, this is a satisfactory explanation of the sudden introduction and wide dissemination of the tick throughout southeastern Montana, but it must be remembered that it is based on no positive data. Southeastern Montana was 30 years or more ago distinctly a horse raising country. This industry was replaced by that of cattle raising, which lasted for only a few years, when the country was turned over to sheep grazing. About 1910 dry farming was first undertaken in this region. Farmers bought up land near water holes and along streams and in their turn the sheep were forced out. Dry farming brought with it necessarily horses and milch cows and the theory given above has, as we have stated, theoretical support.

In Idaho cases seem to be limited to the north side of the Snake River Valley. The disease has been reported in the Quinn River Valley in Nevada, near Meeteetse, Wyo., and in two counties in northern California. In 1915 six cases were reported in the State of Washington, 14 in Colorado, 31 in Utah, and two in South Dakota. The disease has existed since 1903 in Modoc and Lassen counties in California and the adjoining county of Washoe in Nevada. According to Kelly, the disease as it occurs in California is not so severe as that seen in Montana, but is more severe

than that observed in Idaho; in fact, the fatality in the Bitter Root Valley in Montana is higher than in any other locality and it is suspected that these differences in severity are due either to differences in strains of the virus or in species of the tick distributing the virus. Megaw reports a case from India, in which the patient was bitten by a tick at Satal, a place at an altitude of about 5,500 feet, and developed, after an incubation period of 20 days, a disease resembling Rocky Mountain spotted fever. In regard to this case, Megaw says:

"The appearance of a spotty rash at once suggested the spotted fever of the Rocky Mountains, and a reference to the descriptions of that disease showed a close correspondence to the mild Idaho type of that fever. The only point which appeared to be against the diagnosis was the incubation period, which on the assumption that the tick conveyed the disease, must have been 20 days, while most observers place the incubation of the Rocky Mountain fever at three to seven days, Bowers alone placing it at seven to 21 days, but there is evidently a good deal of doubt on the subject."

Eradication.—The Federal and State Governments have devoted much attention to the eradication of the disease from the Bitter Root Valley. Attempts have been made to secure the destruction of the tick. The procedures resorted to for this purpose consist in the following: (1) Cleaning out the underbrush and cultivating the soil. (2) Burning the grass over the valley every spring. (3) Killing small rodents by baiting them with grain which has been soaked in solutions of strychnin. (4) Dipping range stock in tanks filled with arsenical fluids. (5) Sheep grazing. Paine says that when these ticks attach themselves to sheep, their breathing pores are clogged by the lanolin in the wool and they die.

In this disease the tick problem is quite different from that which exists in the form of relapsing fever due to the bite of the African tick. The African tick is a domesticated insect. It lives in the habitations of man and seeks to visit him at night when his deep sleep may prevent interruption of the feeding. In African tick fever disease, man seeks to exclude the insect visitor from his house, his tent, and his blankets. In Rocky Mountain spotted fever the tick is a wild insect. It does not seek the habitations of man; it lives in the wilds and depends naturally for its food upon wild animals. In African tick fever there may be an animal reservoir; in Rocky Mountain tick fever there are many such reservoirs. As has already been stated, many of the small rodents in endemic areas are susceptible to this infection as has been demonstrated experimentally. In these animals the disease so far has manifested itself only in acute form. The animal either dies, or recovers and thereafter is immune. After immunity has thus been induced in these animals their blood is free from the virus. Does it, however, persist in some organ or tissue? This is a question which needs solution. It has been observed that only a small percentage of the ticks found in the Bitter Root Valley bears the virus.

Does this indicate that small rodents in this region are becoming so far immunized that the continued propagation of the virus by natural means will come to an end? Of course, these queries might be answered by saying that every year there are new generations of susceptible rodents coming into existence. There must be some continuous supply of the virus to the tick. In this disease the infection of man is a mere incident or accident and is not essential to the continuance of the disease; in other words, Rocky Mountain spotted fever is a disease of animals to which man also is susceptible, but the disease undoubtedly existed in this locality before man visited it, and the fact that man is susceptible has no essential bearing upon the continuance of the disease.

Bibliography

- ARKWRIGHT, J. A., BACOT, A., AND FUNCAN, F. M.: Trans. Soc. Trop. Med. and Hyg., February 21, 1919.
FRICKS, L. D.: Public Health Reports, 1915, vol. xxx, part 1, Nos. 1-26, page 1694.
KELLY, F. L.: California State Jour. Med., 1916, xiv, 407.
MAXEY, E. E.: Portland Med. Sentinel, October, 1889.
PAINE, L.: Northwest Med., 1916, xxv, 1.
RICKETTS, H. F.: Trans. Chicago Path. Soc., 1906, vii, 73.
WILSON, L. B., AND CHOWNING, W. M.: Jour. Infect. Dis., 1904, i, 31.

CHAPTER XXX

JAPANESE RIVER FEVER

Tsutsugamushi Fever; Shimamushi Fever; Kedani Fever; Flood Fever

Description.—This is a specific, endemic, infectious fever, which follows the bite of the larva of an acarus, *Trombicula akamushi*. From four to ten days after the bite the disease begins with severe headache, accompanied by malaise, anorexia, marked prostration and culminating in a chill, rapidly followed by marked elevation in temperature. There will usually be found on some part of the body evident tenderness of the lymphatic glands, especially in the groin, armpit, or neck. Careful study of this tender region will reveal within its limits one or more eschars, which are closely adherent to the surrounding skin. These indicate the bitten points and when the necrotic eschar drops off there is found under it a small ulcer surrounded by an infiltrated area. The fever continues and may reach 105° F. in its course. The pulse is but slightly accelerated, seldom reaching more than 100 and, as a rule, not keeping up the usual ratio to the temperature. As in many of the infectious febrile diseases, there is a bronchial cough, which may become quite continuous and most distressing. About the seventh day of the fever large red blotches, sometimes confluent, appear on the face and extend to the trunk and extremities. Simultaneous with these blotches there is often a lichenous eruption on the trunk and extremities. This eruption, however, is generally overshadowed by the large dark-red papules and in most cases fades away after a few days. The characteristic eruption, first macular and then papular, begins to disappear during the second week, and simultaneously the temperature falls by lysis. In the majority of instances convalescence is reached before the end of the third week.

There are mild and severe types of this disease. In the latter, symptoms become alarming, the temperature runs so high as to threaten death from hyperpyrexia; there may be pulmonary complications, with edema and cardiac failure. Complications, with parotid inflammation and supuration, have been observed. This disease is highly fatal to pregnant women, most of whom abort and many of whom die.

History.—According to Ashburn and Craig, this disease is described in Chinese writings of more than 1,000 years ago, in which it is designated as “shashitsu.” The Japanese word “mushi” means bug or insect, and “akamushi” means red insect, while “shimamushi” means a disease caused by a bug living on an island.

The first contribution to our knowledge of this disease came from Palm who, in 1878, wrote as follows:

"Last summer, I had the opportunity of observing a disease which, so far as I know, is peculiar to Japan, and has not yet been described. It occurs, moreover, in certain well-marked districts, and at a particular season of the year, so that the opportunities of investigating it do not often occur. It is known here as the *shimamushi*, or island-insect disease, and is so named from the belief that it is caused by the bite or sting of some insect peculiar to certain islands in the river known as the Shinagawa, which empties itself into the sea at Niigata. This river has a strong current, is subject to occasional floods, and being difficult to restrain, is allowed to take its course, eating out its banks on one side, and leaving tracts of new land or islands on the other. It is in these newly-formed soils that the disease occurs. I could find nothing peculiar in the vegetation of these districts. They are partially under cultivation, and the disease occurs among the agricultural laborers who work there, or others who may happen to visit the district at the time. Those are attacked who go among the vegetation, not those who walk along the stony or gravelly banks. The disease occurs only in the months of July and August, especially at the time when the flax plant, which is there much cultivated, is being reaped, and especially among the reapers. The disease is said to be more prevalent in years when the water has been high. It is also said that those who work there only in the early morning or evening are not affected. It is also said that those who are stripped for their work are less frequently affected than those who keep on their clothing. The remarkable thing is, that none of those who are affected are aware at the time of being bitten or stung, and that none of them have ever seen the insect; but the belief universally prevails that it is an insect. At the time of my visit to the spot on August 1st, I could find no one who had seen the insect, though I was told of one man who professed to have seen it, and stated that it was like a small spider. The peasants believe that it is a fine, hair-like worm, of which there are two varieties, the red and the white; but I was unable to discover any foundation for the belief.

"The first symptom of the disease is a hard, round swelling of the skin, like a boil, which is discovered four or five days after having been in the district. Together with this are constitutional disturbance, chills, and feverishness, swelling and tenderness of the glands in the neighborhood of the swollen part. The center of the swelling sloughs and breaks down into an ulcer. Sometimes the tenderness and swelling of the glands is noted before the phlegmon in the skin appears. Sometimes, for a day or two before the swelling is noticed, there is languor, malaise, headache, loss of appetite, and slight feverishness. The fever reaches a maximum at the beginning of the second week, when an eruption appears over the whole body in most cases, after which the fever subsides. Most cases have purging of blood and vomiting and death occurs by exhaustion in three or four weeks from the first symptoms, in fatal cases. It is said that the disease proves fatal in about one-fifth of those attacked. Delirium does not occur, nor are there any symptoms of narcotism even in the worst cases, albumen does not occur in the urine."

A paper, by Bälz and Kawakami, in 1879, gives valuable information on the symptomatology and pathology of this disease, but, so far as its etiology is concerned, its conclusions were erroneous, as subsequent studies have shown. These authors were inclined to disregard the evidence that this disease is due to the bite of the insect and they were of the opinion that it is of miasmatic origin. However, since they found that some peo-

ple who had never visited the fields but handled the flax grown thereon developed the disease, they had to admit that the contagion is transportable. They attempted the inoculation of rabbits and cats with pus and tissue taken from the small ulcers, but in this they were unsuccessful.

In 1908 Ashburn and Craig visited Japan for the purpose of studying this disease and making comparisons of it with Rocky Mountain spotted fever. We quote:

"*Tsutsugamushi* disease occurs along certain limited parts of the banks of a few rivers on the west coast of the main Island of Nippon, being limited to Echigo and Akita Provinces. The distribution of the infected areas is irregular and, up to the present time, inexplicable. They are all subject to submergence by floods which occur in June, but not all flooded districts are infected, nor does the relative location of an infected district, up or downstream, seem to influence a noninfected one. The floods usually occur in June and last but a few days. Immediately after their subsidence the infective regions are not dangerous, but after a few weeks or a month and synchronously with the appearance of the *akamushi* or red mite, they become so, and any person entering them takes a considerable risk of contracting the disease. Consequently, these regions are avoided at this time by all whose poverty does not drive them there to work. As a general rule no right of ownership is exercised over such land and the very poor do, therefore, cultivate hemp on it in some places and in other parts visit it to gather mulberry leaves to feed silkworms. In either case they are apt to be bitten by red mites and it is customary for them to search carefully for their bites after leaving the place where they are encountered. However, the mites are so small as to be very difficult of detection and if the bite does not cause pain, it is frequently overlooked. Not all mites are infective and many bites therefore cause no trouble. However, a certain proportion of them do, the point bitten becoming an eschar and later an ulcer. The neighboring lymphatic glands become enlarged and painful and an attack of fever succeeds.

"It is the experience of practically all who have carefully studied the disease, and they are numerous, that *every* case of it is preceded by the bite of a mite, and in the great majority of instances this is located by an examination of the region drained by the lymphatic glands, which first become enlarged and tender. So far as could be learned in Japan, Bälz's contention that such is not the case has not received support, and later investigators agree that the above method is the sole means of infection. The mite in question is the larval form of a *Trombidium*, species unknown. The larva bears a great resemblance to that of *Leptus autumnalis*. It is so small as to be almost invisible to the naked eye, it is bright red or orange in color and is found on land that has been submerged by flood. Here it is best collected by tying a monkey out overnight or by catching the field mice (*Arvicola hatanadzumi*) occurring in such regions. The insects collect in groups on or about the eyelids of the monkey, while they are always found attached in large numbers to the inner surfaces of the ears of the mice. Mites resembling these in size and color occur in many parts of Japan, but they do not attack persons. The *akamushi* of other than infected regions do not transmit disease."

It is worthy of record that Ashburn and Craig did not find any relation between this disease and Rocky Mountain spotted fever. On the other hand, they pointed out the marked differences between the two in etiology, symptomatology, pathology, and immunology. These investigators then asked themselves whether there is in the Philippine Islands any disease

resembling that which they had studied in Japan. They state that at Camp Connell on the west coast of Samar where a target range is located the physical conditions, including the annual overflow, resemble closely those of the endemic Japanese areas. Furthermore, they report that two cases with some resemblance to the Japanese disease occurred among troops stationed at Camp Connell in 1905. They do not maintain that the cases developed at Camp Connell were those of the Japanese disease, but they point out that the resemblance is sufficient to make medical men in the Philippines bear in mind the possibility of the Japanese disease occurring in these Islands.

According to Hatori, the river fever is widely diffused in Formosa, where it occurs not only on the lowlands, but in high altitudes and affects both the natives and the Japanese settlers. In Formosa the disease is first seen in April and disappears in November. Writers on this disease have referred to an article by Weir on, "A Continued Fever of Korea" as evidence that the Japanese river fever exists in Korea. We have read Weir's article carefully and fail to see any resemblance, or at least any marked resemblance, between the disease which he describes and that prevalent in western Japan. Weir discusses in some detail the nature of the Korean disease and comes, as we think, to the very tenable conclusion that it is a mild form of typhus, for which he proposes the name paratyphus.

The Mite.—The life-cycle of this insect has been investigated by Japanese scientists and it has been found to be the larva of *Trombicula akamushi*, a mite which measures 0.9 mm. in length, is not parasitic, and lives on grass. Blood from men sick with this disease injected into small rodents and monkeys conveys the disease to these animals. The amount of such blood required to infect a monkey is as small as 0.001 c.c. The infection in the blood is destroyed by heating to 50° C. for ten minutes. While, as has been stated, this mite gathers in large numbers in the ears of field mice and other small rodents, it has not been found that these animals are in any way affected. It is said that the mite is distributed by a small bird, *Acrocephalus orientalis*.

Nagayo and his coworkers have shown that there are at least five species of *Tsutsugamushi* in Japan, but that only one of these, *Tr. akamushi*, induces the disease and that it is only the larva of this species which bites man. The adult insect contains the virus, as these investigators have shown by injecting subcutaneously emulsions of the ground insects into monkeys. The adult and the nymph are not noxious to man, not because they do not carry the specific virus, but because they do not feed upon warm-blooded animals.

Miyajima and Okumura trace the life-history of this insect as follows:

"The *akamushi* remains on the host for three or four days and swells up considerably, turning much paler in color. When fully fed the mite frees itself from the host

and seeks shelter under the ground. Then a gradual metamorphosis takes place in five or six days (in a hot climate); the new parts of the nymph develop within the larval skin. Two to three days later the larval skin bursts and the nymph emerges. The newly hatched nymph is a minute, eight-legged creature quite different from the larvae. The size of the young nymph does not exceed that of the full fed larvae. In the culture jar the mites are seen to crawl lively in the earth; sometimes they even try to get out of the vessel. They are neither parasitic nor predaceous. After a number of trials, we succeeded in finding that their suitable food is potatoes, melons, and other vegetables. The mites like the juice of vegetables, but seem to dislike sour fruit like apples and oranges. Proper amount of moisture is a *sine qua non* condition to keep the nymph healthy and to carry it to the adult. So jars are always kept in moist chambers during the growing stages of the mites. When they have grown to a certain stage they again seek shelter in the earth where pupation takes place. The body of the nymph becomes elongated; so also with its mouth part and the appendages. Most parts of the body develop within the nymphal skin and in a few days later the adult form emerges. Newly appeared imago shows a close resemblance to the nymph in form and structure, but it is much larger. By this time the genital organs begin to develop, but do not ripen. There are no visible sexual differences until the maximum size and maturity is attained. It seems probable that more than one ecdysis takes place. Direct observations could not be made because of the difficulty of distinguishing each stage. They have variable body sizes and different pupation periods. In ten weeks' captivity the nymph becomes an imago, measuring 0.84—0.98 mm. in length. Only a few of them, however, live long enough to attain maturity. One of the survivors was a female which attained a fully developed ovum measuring 0.18 mm. in diameter. We have thus successfully traced the whole developmental cycle of the 'akamushi' from the larval form to the adult. Having thus discovered the adult form of the 'akamushi,' we then tried to study the adults in their natural habitat in one of the infected localities, Niigata Prefecture, where an enormous number of the mites (larval stage) was met with every summer. During September, 1916, we collected a large number of the adults and the nymphs there, and at the same time have learned a great deal of their ecology. They are usually found under fallen leaves or decayed vegetable matters in the grass over the fine sandy mud precipitated by floods. When exposed the mites would briskly seek their shelter in the earth; it is probable that they tried to avoid direct sunlight and desiccation. In a certain uncultivated spot they were found so abundantly that one bushel of the surface earth covering one square yard contained about fifty specimens. In nature, both the nymph and the adult seem to live on the juice of plants.''

The Virus.—While there have been many attempts made to discover the virus of this disease and repeated theories and findings have been published, there is nothing absolutely convincing up to the present time. Tanaka suggested that the disease might be due to a poison peculiar to the insect, but this cannot be true, since bites by the same species of insect in other parts of Japan are without effect. Other investigators have reported the finding of bacteria; others still, protozoa and piroplasma.

Prophylaxis.—Avoidance of infested localities during the season of the prevalence of the mite is up to the present time the only known absolute method of prevention. A mite-proof suit has been devised by two Japanese physicians and they recommend that all articles of clothing worn by those who work in endemic localities should be sterilized. Others

recommend that rivers be dammed and overflow checked in this way. Disinfectants have been scattered over the infested fields and some recommend that those who are compelled to go into endemic areas should anoint their bodies with balsam of Peru to which certain phenol preparations have been added. At one time Bälz urged that the endemic areas should be planted with eucalyptus, but this recommendation was made with the belief that the disease was of miasmatic origin and was at a time when eucalyptus was regarded by many as a panacea for converting malarial regions into healthful countries.

Bibliography

- ASHBURN, P. M., AND CRAIG, C. F.: *Philippine Jour. Sc.*, 1908, iii, 1.
BÄLZ, E., AND KAWAKAMI: *Virchows Archiv.*, 1879, lxxviii, 373.
MIYAJIMA, M., AND OKUMURA, T.: *Kitasato's Arch. Exper. Med.*, 1917-1918, i, 1.
NAGAYO, M., AND Co-WORKERS: *Am. Jour. Hygiene*, 1921, i, 569.
PALM, T. A.: *Edinburgh Med. Jour.*, 1878, xxiv, 128.
WEIR, H. H.: *China Med. Jour.*, 1915, xxix, 307.

CHAPTER XXXI

TULAREMIA

Description.—This is a specific, infectious, highly fatal, septicemia, which occurs among certain rodents, ground-squirrels, and rabbits in their natural wild state. Mice, gophers, rats, monkeys, and guinea pigs are susceptible in the laboratory. This infection also prevails in man in nature in communities where there are infected rodents. The infecting agent is *Bacterium tularense*.

History.—In 1910 McCoy, while studying the plague among wild rodents of California, found many of these animals infected with a disease, the pathologic lesions of which greatly resemble those of plague but in which the plague bacillus cannot be found. McCoy summarized his observations on this disease as follows:

“A disease which presents lesions very similar to those of plague has been found among ground-squirrels. The disease is readily transmitted to guinea pigs, mice, rabbits, monkeys, and gophers, and plague-like lesions are produced in at least some of these animals. Rats are but moderately susceptible to the infection. Cats, dogs, and pigeons appear to be immune. The disease may be transmitted artificially by subcutaneous, cutaneous, nasal, and intraperitoneal inoculation. The mode of transmission in nature is unknown, but there is some experimental evidence that suggests that fleas may serve as carriers. The disease probably is not spread by mere contact of healthy with infected animals. The infectious agent has not been isolated. On account of the number of species susceptible, it seems likely that it is bacterial, not protozoan. The causative agent is present in the circulating blood, as well as in the various tissues where it causes focal lesions. The thermal death point of the organism as it is found in the animal's body is between 55° and 60° C. Several observations appear to indicate that the disease is a febrile one.”

This work was continued by McCoy and Chapin, who succeeded in demonstrating that this infection is due to a small bacterium which they were able to cultivate on a special medium, coagulated egg yolk. They also showed that cultures of this organism are agglutinated by the serum of artificially or naturally immune animals, while they are not agglutinated by the serum of healthy susceptible animals. It appears that the sub-acute and chronic lesions of this disease bear a strong resemblance to those of tuberculosis.

In 1913 Wherry and Lamb saw the first reported case of this infection in man. The patient was a meat cutter in a restaurant in Cincinnati. It is said that at the time wild rabbits were dying in large numbers across the Ohio River in Kentucky. This man evidently received his infection through the eye. On the conjunctiva covering the upper and

lower tarsi there were ten discrete ulcers varying from 1 to 4 mm. in diameter. The lids were edematous and the preauricular gland on the left side was tender and swollen. The edema increased, the ulceration became more marked, and the lymphatic glands in the left anterior triangle of the neck and the left submaxillary glands became tender and swollen. Four days after admission to the hospital the patient's temperature was 101.6° F. He had a cachectic look and was losing weight. About this time a pustular eruption appeared on the left temporal and malar regions. After a few days more, the inflammatory process spread to the left lacrimal sac and an abscess formed. Scrapings from the ulcers injected into guinea pigs proved fatal and autopsy revealed lesions identical with those previously reported by McCoy. After being under observation for a month the patient left the hospital and apparently was lost sight of. Wherry and Lamb summarize their observations as follows:

"A case of ulcerative conjunctivitis and lymphadenitis in man is shown to be caused by a minute, capsulated bacterium in all probability identical with *B. tularensis*, which was first discovered by McCoy and Chapin in a plague-like disease of the California ground-squirrel. Without the employment of very special methods of staining and cultivation, the virus, although it was known not to pass the Berkefeld filter No. 5, remained invisible. We recommend anilin-water-Hoffman's violet, particularly for its demonstration, and in addition to the coagulated hen's egg-yolk recommended by McCoy and Chapin for its cultivation, we find that hen's ovomucoid with a trace of yolk is also a favorable medium. Our findings would seem to indicate that this disease is widespread among rodents. Further, we wish to call attention to the fact that this recently discovered disease of rodents is apparently sufficiently virulent for gray mice to warrant the presumption that it may some day take its place with *B. pestis* as a menace to man."

Further studies on this disease have been carried out by Francis and other officers of the U. S. Public Health Service. From 1917 to 1920 inclusive, about 24 cases in human beings occurred in Millard County, Utah, annually. The first fatal case among men was reported in that region in 1919. Even when not fatal, tularemia is a serious disease, since it occurs quite exclusively among farmers during the busy season of midsummer and incapacitates its victim for about three months. All the officers and laboratory assistants of the Public Health Service, six in number, who have been intimately connected with the study of this disease have become infected with the bacterium. This record is probably unequaled in the history of the study of any other infectious disease and indicates the high infectivity of the organism and the great susceptibility of man. Two of these officers contracted the disease in the Field Laboratory in Utah, where they were compelled to work under primitive conditions, but four contracted it in the Hygienic Laboratory at Washington, where every precaution against infection was provided for. Two of these men were physicians of long experience in working with infectious diseases, one was

a highly trained scientist, and the other three were experienced laboratory assistants. Known foci of this infection in rodents have been reported from California, Utah, and Indiana, and there are probably many other infected localities. It is more than probable that human infection has often been unrecognized. The symptoms in these six officers have been carefully studied. The diagnosis has been confirmed by agglutination and complement-fixation tests. There is a febrile period lasting about three weeks. It is supposed that the bacterium finds its way through the hands. In one case there were evident cracks on the fingers of the right hand and in this instance the infection was followed by enlarged, painful and tender lymph glands in the epitrochlear and axillary regions of the right side. This man had had an attack two years and five months previously.

It has been experimentally demonstrated that this infection may be transmitted from animal to animal by certain biting flies, by fleas, by lice, and by bedbugs. Virulent organisms have been demonstrated in the fresh feces of infected bedbugs constantly up to eight months after the date on which the bugs sucked the blood of an infected mouse. It is interesting to note that the infection from the bedbugs may result either from the infected bug biting the mouse or from the mouse eating the infected bug. Seventy-two white mice ate dying or dead bugs from each of ten infected lots; of these, 55 died from tularemia. It seems that white mice eat bedbugs quite greedily. These investigations revealed the fact that white mice carry a blood-sucking louse, *Polyplax serratus*, and a blood-sucking mite, *Liponyssus isabellinus*, both of which may transfer this infection from mouse to mouse. Rabbits carry both blood-sucking fleas and lice, and it was found that if the hair over the lumbar and sacral regions of an infected rabbit were clipped and transferred to a noninfected comrade the disease was transmitted. Both the nasal secretions and urine of infected rabbits contain the virus. The vector most commonly effective in transmitting this disease from wild animals to the farmer is quite certainly some blood-sucking fly, such as *Chrysops discalis* or *Stomoxys calcitrans*. In the Utah cases in man, there were invariably found a pronounced lesion at the site of infection and an enlargement of the adjacent lymph glands. This, however, was not the case in at least all of the six laboratory workers studied.

The Bacterium.—*B. tularense* is a minute rod, probably enclosed in capsular substance as seen in infected tissue. It is most frequently seen first as a coccoid body. McCoy and Chapin give the following approximate measurements: Length, 0.3 to 0.7 micron; length of capsule, 0.4 to 1 micron; breadth, 0.2 micron; breadth of capsule, 0.3 to 0.5 micron. No distinct capsule can be seen in artificial cultures. As has been stated, it grows quite readily on coagulated egg yolk and less readily on other

media containing egg yolk. The investigations of Francis show that this bacterium may be grown on serum glucose agar, glucose blood agar, and blood agar; but on these, growth is scanty and of low virulence. The addition, however, to these media of a piece of fresh sterile rabbit spleen or of a piece of the spleen of an infected animal, stimulates the growth and intensifies the activity of the organism. Francis has recently reported the growth of this organism on plain agar to which has been added .02 per cent of the amino acid, cystin. Serum glucose agar, containing .02 per cent cystin, gives a luxuriant growth.

Prevention.—Fortunately, there are not many biting insects which feed with equal readiness upon man and small rodents. If there were such insects, tularemia might become a widely prevalent disease of man. Infested localities should be sought out, the animals susceptible to this disease and the insects engaged in its transmission should be thoroughly studied, and upon this we may base some effective method of control. It certainly should be understood that during the warm season of the year especially, it is unwise to handle wild rodents; for instance, rabbits, since at this time they are rich in blood-sucking insects. Laboratory workers should avoid the contact of infected tissues with their hands; this is best done by wearing gloves.

Bibliography

- FRANCIS, E., AND LAKE, G. C.: U. S. Public Health Reports, July 29, 1921; January 20, 1922; February 24, 1922; April 28, 1922; Jour. Am. Med. Assn., 1922, lxxviii, 1015.
- McCoy, G. W.: U. S. Public Health Bulletin, 1910, No. 43.
- McCoy, G. W., AND CHAPIN, C. W.: U. S. Public Health Bulletin, 1912, No. 53.
- WHERRY, W. B., AND LAMB, B. H.: Jour. Infect. Dis., 1914, xv, 331.

CHAPTER XXXII

THE PLAGUE

The Pest; the Black Death

Description.—This is an acute, highly infectious, markedly fatal, disease which has been known to the world mostly in epidemic form. It results from infection with a specific microorganism, the *Bacillus pestis*. It manifests itself in two forms, the bubonic and the pneumonic. The fatality of the former varies greatly, while it is rare for one to recover from the latter.

History.—The Valley of the Nile is now generally believed to have been the site of the earliest development of civilization. It appears that the Egyptians of the time of the earlier Pharaohs drained the land, built aqueducts, disposed of their dead hygienically, reared temples, maintained law and order, developed the elements of literature and science, and devised and employed simple machinery. In speaking of the Egyptians of this remote time, Diodorus says:

“The whole manner of living was so evenly ordered that it would appear as though it had been arranged by a learned physician rather than by a lawgiver.”

Herodotus declared ancient Egypt the healthiest of countries, but filled with physicians, of whom “one treats only the diseases of the eye, another those of the head, the teeth, the abdomen, or the internal organs.” We are inclined to suspect that the above-given quotations are exaggerations; but that ancient Egypt was a fairly healthy country in which the manhood of the time was strong and vigorous and the race was for a long time without the scourge of severe epidemics, seems to be substantiated by the testimony of many. It is quite equally certain that preceding and at the time of the exodus of the children of Israel, Egypt was visited and devastated by repeated and deadly epidemics. In other words, it is evident that in the time of its greatest civilization Egypt was salubrious, and that coincident with the decline in the learning and wisdom of its people it was ravaged by pestilence. That Egypt had lost much of its salubrity as early as the exodus of the children of Israel is indicated by many passages in the Bible, in which the chosen people are threatened with the diseases of Egypt if they neglect or violate the laws. Moses “learned in all the wisdom of the Egyptians” codified his sanitary rules and regulations in the form of religious rites and ceremonies and thus secured their observance among the faithful, even down to the present time. After the departure of the chosen

people it seems that Egypt has continuously borne an evil reputation so far as health is concerned. Gibbon wrote:

“Ethiopia and Egypt have been stigmatized in all ages as the source and seminary of the plague.”

Stricker is quite sure that the pest among the Philistines described in the first book of Samuel, when the captured ark was returned with five golden emerods and five golden mice, was the bubonic plague.

Thucydides has left a graphic description of the great Athenian plague, but he has left room for controversy as to the exact nature of the disease. His description is not sufficiently clear to justify a positive conclusion. After reading it, one concludes that it must have been either typhus fever or the pneumonic form of the plague. Probably the weight of evidence is in favor of the latter opinion.

The time of the earliest appearance of the plague in Italy is not known. It is certain that it was quite well established in the peninsula in the first century of the Christian era, and in all probability this was not the first visitation. Unfortunately, the historian, as a rule, confines his description to martial and political events, and consequently it often happens that he gives a wholly erroneous idea of the true condition of the people. Gibbon says:

“If a man were called upon to fix the period in the history of the world, during which the condition of the human race was most happy and prosperous, he would without hesitation, name that which elapsed from the death of Domitian to the accession of Commodus” (from 96 to 180 A. D.)

Noah Webster, in his work on epidemics and pestilence, quotes the preceding, and adds the following just comment:

“It is certain that, at this time, the Roman Empire was in its glory, and governed by a series of able and virtuous princes, who made the happiness of their subjects their principal object. But the coloring given to the happiness of this period is far too brilliant. The success of armies and the extent of empire do not constitute exclusively the happiness of nations; and no historian has a title to the character of fidelity, who does not comprehend, in his general description of the state of mankind, moral and physical, as well as political evils.”

It may be profitable to make some inquiry as to the diseases which prevailed in this “most happy and prosperous” period. We find that it was preceded by, begun in, continued in, and closed in, pestilence. Evidence of the truth of this statement is furnished by the great historian Tacitus, who wrote of the epidemic of 68 A.D. as follows:

“Houses were filled with dead bodies and the streets with funerals; neither age nor sex was exempt; slaves and plebians were suddenly taken off, amidst lamentations of their wives and children, who, while they assisted the sick or mourned the dead, were seized with the disease, and perishing, were burned on the same funeral pyre. To the knights and senators the disease was less mortal, though these also suffered in the common calamity.”

In the year 80 A.D. deaths from the plague in Rome alone at the height of the epidemic numbered 10,000 a day. It is estimated that the population of Rome at that time was something more than 1,000,000. Rufus, of Ephesus, who lived in the reign of Trajan (98-117 A.D.), has left a description of the epidemic of his time, and this is so clear and unequivocal that there can be no doubt about its being the disease which we are now describing. He wrote: "*Pestilentes bubones, maxime letales et acuti, qui maxime circa Lybiam, et Aegyptum et Syriam observantur.*"

Exacerbations of this disease in Rome are recorded for the years 102, 107, and 117 A.D. The year 167 A.D. is noted for an unusually severe outbreak of the plague at Rome, where it continued for many years. In 173 A. D. the Roman Army was threatened with extinction by this disease, and special epidemics, or rather exacerbations of the same epidemic, prevailed in the city in 175 and 178 A.D.

During this time the plague was not confined to Rome or to Italy, but it accompanied the Roman eagle to the most distant parts of the vast empire. According to Short, deaths from this disease in Scotland between 88 and 92 A.D. amounted to not less than 150,000. This was probably not less than one-fourth, and probably one-half the population of Scotland at that time. According to the same authority, 45,000 died of the plague in Wales in 114.

Having seen something of the condition of the Roman Empire preceding and during the "happy and prosperous" period, let us inquire as to what followed it. A writer of that time states:

"A great pestilence raged throughout Italy at that time (about 187 A. D.) but with most violence in the city, by reason of the great concourse of people assembled from all parts of the earth. The mortality among men and cattle was great. The emperor, by advice of physicians, retired to Laurentium, on account of the coolness of the place, which was shaded with laurels. It was supposed that the fragrance of the laurels acted as an antidote against contagion. The people in the city, also, by the advice of physicians, filled their noses and ears with sweet ointments and used perfumes, etc."

When we read the gems of wisdom, said to have been formulated by that great emperor and philosopher, Marcus Aurelius Antoninus, we are inclined to think that the period when he sat on the throne of the world deserves to be called the golden age. It is with special interest, therefore, that we read what his personal attendant, courtier, and historian wrote in extolling the virtues of his master:

"Unless he, M. Antoninus, had been born at this juncture the affairs of the empire would have fallen into speedy ruin, for there was no respite from military operations. War raged in the east, in Illyricum, in Italy, and in Gaul. Earthquakes with destruction of cities, inundations of rivers, frequent plagues, a species of locust ravaging the

fields; in short, every calamity that could be conceived to afflict and torment man scourged the human race during his administration.”

The physician and historian, Procopius, in his account of the great pestilence in the reign of Justinian “emulated the skill and diligence of Thucydides in the description of the plague at Athens.” Founded upon the evidence supplied by the writings of Procopius, Gibbon wrote of this epidemic as follows:

“In time its first malignancy was abated and dispersed; the disease alternately languished and revived, but it was not till the end of a calamitous period of 52 years, that mankind recovered their health, and the air resumed its pure and salubrious quality. No facts have been preserved to sustain an account, or even a conjecture, of the numbers that perished in this extraordinary mortality. I only find that during three months, four and at length ten thousand persons died each day at Constantinople, that many cities of the east were left vacant, and that in several districts of Italy, the harvest and vintage withered on the ground. The triple scourge of war, pestilence and famine afflicted the subjects of Justinian, and his reign is disgraced by a visible decrease of the human species, which has never been replaced in some of the fairest countries of the globe.”

This epidemic spread from Constantinople over the whole of Europe slowly as the means of travel furnished opportunity. It turned aside into out-of-the-way recesses wherever necessity or inclination led its carriers. It took it more than a century to reach England, where “it fabled long after in prose and verse as the great plague of Cadwalader’s time.” Then for more than a thousand years it repeated its periodic harvests as often as immunity was lost in new generations.

In the fourth century the seat of the imperial government was removed from Rome to Byzantium. It is probable that this change was, in part at least, determined by the insalubrity of Italy. Early in the fifth century Rome was pillaged, but the real conquerors of the Eternal City were not the Goths and Vandals, but malaria and the plague. Disease continued to devastate the peninsula. Creighton says:

“About the year 668 the English archbishop-elect, Vighard, having come to Rome to get his election confirmed by the pope, Vitalianus, was soon after his arrival cut off by the pestilence with almost all who had gone with him. Twelve years after, in 680, there was another severe pestilence in the months of July, August, and September, causing a great mortality at Rome and such a panic at Pavia that the inhabitants fled to the mountains. In 746 a pestilence is said to have advanced from Sicily and Calabria and to have made such devastation in Rome that there were houses without a single inhabitant left.”

Periodically, from that time on, the plague visited Italy until the seventeenth century, while malaria has been in continuous possession of its most fertile regions down to our own time. We are informed that the plague epidemic in 1348 reduced the inhabitants of the Eternal City to 20,000. We are familiar with the graphic description of the plague in Florence by Boccaccio, who wrote:

"Such was the cruelty of Heaven and perhaps of men, that between March and July following, it is supposed and made pretty certain, that upwards of 100,000 souls perished in the city only, whereas, before that calamity, it was not supposed to have contained so many inhabitants. What magnificent dwellings, what noble palaces were then depopulated to the last person, what families extinct, what riches and vast possessions left, and no known heir to inherit, what numbers of both sexes in the prime and vigor of youth—who in the morning Galen, Hippocrates or Esculapius himself, would have declared in perfect health—after dining heartily with their friends here have supped with their departed friends in the other world."

Guy de Chauliac, body physician of Clement VI (pope from 1342 to 1352), recognized the two forms of the plague. He wrote:

THE SECOND PANDEMIC OF PLAGUE EXTENSION OF THE DISEASE BETWEEN 1200 - 1450. A.D.



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Fig. 50.

"*Pestis habuit duos modos. Primus fuit per duos menses cum febre continua et sputo sanguinis. Et isti moriebantur infra tres dies. Secundus fuit per residuum temporis cum febre etiam continua et apostematibus et anthracibus in exterioribus, potissime in subasellis et inguinibus. Et moriebantur infra quinque dies. Et fuit tantae contagiositatis, specialiter quae fuit cum sputo sanguinis, quod non solum morando, sed etiam inspicendo unus recipiebat ab alio.*"

In the wide range of literature there are but few passages so tragic as the short record of the plague of the fourteenth century begun by the friar of Kilkenny, but interrupted by his death:

"I friar, John Clyn, of the order of Friars Minor and of the convent of Kilkenny, wrote in this book those notable things which happened in my times, which I saw with my eyes, or which I learned from persons worthy of credit. And lest these things worthy of remembrance should perish with time and fall away from the memory of those who are to come after us, I, seeing these many evils, and the whole world lying,

as it were in the wicked one, among the dead, awaiting death—as I have truly heard and examined, so have I reduced these things to writing; and lest the writing should perish with the writer, and the work fail altogether with the workman, I leave parchment for continuing the work, if haply any man survive, and any of the race of Adam escape this pestilence and continue the work I have commenced.”

It is estimated that during the dark ages the average of human life was less than 20 years. A high birth rate was necessary to keep the race alive, but notwithstanding this, Europe was sparsely inhabited. At the time of the Norman conquest the inhabitants of England numbered between two and two and one-half million,—probably nearer the former, for they had not reached the greater number a hundred years later. Creighton says:

“It would be within the mark to say that less than one-tenth of the population was urban in any distinctive sense of the term. After London, Norwich, York, and Lincoln, there were probably no towns with 5,000 inhabitants.”

Indeed, urban life, as we now know it, was quite impossible in this age of pestilence and would soon become so again were the functions of preventive medicine relaxed.

Nankivell writes of the plague in England in the fourteenth century as follows:

“The distribution of the mortality was various. Those of high rank were not greatly affected, but of the common people an incalculable number died, and very many of the clergy, nuns, and friars. The religious houses seem especially to have been severely visited by the Black Death, and many of them were closed and left deserted. The records of mortality in those days were indifferently kept, and it is most difficult to arrive with any accuracy at an estimate of the number of those who died of the plague. Contemporary writers vary in their estimates from one-fifth to nine-tenths of the total population as the extent of the mortality, but it is probable that between half and two-thirds would be a more accurate estimation. In other words the death rate in England during the years of the Black Death was somewhere near 600 per thousand persons living! It is probable that about 20,000 persons died in London out of an estimated population of 40,000. In Leicester there were about 1,500 deaths among a population of under 4,000 persons. In Bodmin there were the same number of deaths out of a population of some 3,000 people. Norwich had, perhaps, 17,000 deaths out of a population which was probably about 25,000, although in the borough records the mortality was stated to be over 57,000, which is manifestly exaggerated. Yarmouth lost 7,000 of its 12,000 people. As far as we can read from the scarce records, mortality of a like nature was present through the length and breadth of the land. Business was dislocated; cattle and sheep were left to wander, for there was no one to care for them, and a murrain occurred among the beasts. As half the labor in the country was dead, wages rose to an unprecedented height, and, according to Creighton, many villeins and bondsmen took the opportunity of escaping to the towns or to distant manors, where they could make their own terms. The Black Death was, therefore, the last nail in the coffin of the old feudal system.”

Most of the great epidemics of the middle ages were designated as *pestilentia* or *magna mortalitas*. In the most deadly visitations, the

bubonic plague is so accurately described that there can be no doubt about its identity; but it must not be supposed that the people enjoyed any high degree of health even in those periods when this contagion languished on account of exhaustion of susceptible victims. Ergotism, under the name of Saint Anthony's fire, was endemic in France and adjacent territories; Normandy was filled with lepers; but Christ's poor were not confined to that country. England was regarded as the special home of hunger, but abundance was a stranger to the masses in every land. The mysterious sweating sickness, apparently brought to England with Henry Tudor in 1485, developed in five distinct epidemics, which were characterized by the fact that the mortality was greater among the rich than among the poor. Typhus, known as *morbus pauperum*, prevailed largely in the jails, on ships, and among the squalid inhabitants of the cities. It is held by many eminent authorities that the discovery of America carried to Europe the scourge of syphilis, which was spread over Italy by the soldiers of Charles VIII, and within a few years reached the most distant parts of Europe. Smallpox appeared in England in the sixteenth century, having journeyed, according to the most reliable authority, all the way from the Orient. That tuberculosis, diphtheria, dysentery, and other diseases still with us, prevailed during the middle ages is shown by the records, but they were overshadowed by the higher mortality of those mentioned above. Improved agriculture has extinguished the fire of Saint Anthony, except in the most benighted provinces of Russia. The great fire in London in 1666 destroyed the infected rats and relieved England of the bubonic plague, which had been endemic in that country since 1349. Something more than 100 years later the discovery of Jenner robbed smallpox of its horrors wherever vaccination is properly enforced. The investigation of Howard improved the sanitation of jails and workhouses and did much to eradicate typhus.

Thirty-two deaths from plague are noted in the U. S. Registration Area from 1911 to 1919 inclusive. One death occurred in 1911, 2 in 1913, 10 in 1914, 1 in 1915 and 18 in 1919. In the last mentioned year 13 of the deaths are charged to California.

Bacillus.—This was discovered and isolated by Yersin and Kitasato independently in the epidemic in Cochin China, and at Hongkong (1893-1894). Since the description given by these investigators did not agree in every detail, it was suggested that the organisms obtained by them are not identical; but subsequent studies have shown that they are only slightly different strains of the same bacterium. The bacillus is a short, plump rod with rounded ends and stains more deeply at the ends than in the middle—bipolar staining. In length it varies from 1.5 to 1.7 of a micron and its breadth is about one-third its length; however, it

manifests marked morphologic variability, coccus-like forms and long rods being found in the same body, also in the discharge from buboes and in the sputum. The polymorphic growth of this bacillus must be held in mind in making a microscopic diagnosis, which is easily done by an expert. It takes the basic stains, such as methylene-blue, quickly and deeply. Gaffky recommends that the dried smear be washed with 0.5 per cent of acetic acid before the stain is applied. It is non-motile, nonliquefying, and may show a mucous capsule. This, however, is often not recognizable unless it be brought out by special methods. In the first description of his find, Kitasato made it a motile organism, but subsequently it was shown that such motility as it may manifest is wholly passive. It is sporeless, but may remain viable in culture for four years.

Most pathogenic bacteria have their optimum growth temperature at, or slightly above, that of the animal body. This is not true of the plague bacillus. It grows at the temperature of man's body; otherwise, it could not be pathogenic to man; but in artificial cultures it grows rapidly and abundantly some degrees lower. It grows, but less rapidly still, at febrile temperatures. It develops on neutral and feebly alkaline media and is an aerobe. On gelatin plates at 22° C. (71.6° F.) it develops within three days fairly characteristic colonies. The superficial ones project above the surface, are coarsely granular and partially transparent. They do not liquefy the gelatin and the deep colonies are in no way characteristic. In gelatin stick cultures, this bacillus grows slowly, but uniformly along the line. In undisturbed bouillon, a deposit forms; later the surface is covered, and stalactites and stalagmites may develop; however, these formations, although striking, are not confined to cultures of the plague bacillus. Hankin uses for diagnostic purposes an agar containing from 2.5 to 3.5 per cent of salt. On this medium well-marked involution forms develop. Swollen, spindle-shaped, and ovoid forms appear instead of the normal rods. Other investigators claim that other bacteria grown on this medium develop similar forms and that this test should not be relied on for diagnostic purposes; however, this is largely a matter of expert training. Hankin, in the midst of the plague in India, has in all probability acquired an expertness which a European laboratory worker with only old cultures at hand is not likely to secure after a short series of tests. The plague bacillus grows abundantly on coagulated serum, but offers nothing distinctive in such growths. It multiplies slowly in sterilized milk without coagulation, although there is a slight development of acid. In pepton solution and on potato its growth is slow and nondistinctive.

The bacillus may retain both vitality and virulence for a long time in men and rats recovered from the disease. The organisms carried by

these hosts, however, are not always virulent. Moreover, as a rule, men and animals recovered from the disease are free from the bacillus. Strong found that avirulent bacilli injected subcutaneously into apes are wholly destroyed within 24 hours. As has been said, cultures protected from drying and from the light may remain viable after four years and, indeed, they have been reported as still virulent. Old subcultures after many years become quite inert. While complete desiccation soon destroys the bacillus, so long as moisture persists, its destruction within a reasonable time is improbable. From this we may deduce two practical lessons. The first is that plague pus or sputum deposited on clothing may retain its vitality for months. The second is that air-borne infection does not play an important rôle in the distribution of this disease. The last statement must not be taken as denying the possibility or even the probability of droplet infection, especially in pneumonic cases. Direct sunlight kills speedily, the time varying with the thickness of the layer. Speaking generally, hours are necessary. An agar culture exposed to direct sunlight contains virulent bacilli after two hours and bubonic pus placed on glass and exposed directly to sunlight is nonvirulent after about six hours. Bouillon cultures used for immunizing purposes are sterilized by heating for one hour at 58° C. (136.4° F.). Boiling kills in one minute. Dry heat at 100° C., continued for one hour, kills the bacillus. Ordinary methods of disinfection suffice to destroy this organism.

The virulence of this bacillus is quite variable. It is probably true that the bacterium from any animal dead of this disease is pathogenic to the rat and guinea pig, but some strains retain their virulence through many generations when grown artificially, while others lose it. The virulence is more quickly lost at incubator than at lower temperature. In order to preserve the virulence of cultures, passage through susceptible animals should be resorted to from time to time. Repeated animal passage may revive a failing virulence.

All rodents are susceptible to the plague bacillus, but between the different species of these there are wide variations. The most susceptible is the rat, which suffers extensively from epidemics of this disease and responds to every form of artificial inoculation. When the plague virus is rubbed into the shaved or clipped abdomen of this animal the bacillus finds its way through the skin, apparently when there is no injury, and causes a general infection. When the skin is pricked with the finest infected needle, the nearest glands become swollen and the neighboring tissue edematous, while the infection extends to other glands and soon a general infection is established. The spleen is enlarged, the lungs and liver become hyperemic and after death the bacillus is found in every part of the body. When the injection is

made into the peritoneal cavity, the bacillus passes through the peritoneal walls, which seem only somewhat more moist than normal, and reaches the various organs. Given by mouth, the first visible effect may be an enlargement of the cervical glands, or the mucous membrane of the stomach and small intestine may become inflamed and hemorrhagic and the mesenteric and other glands may be enlarged. Either form of the disease may develop and in any case the disease terminates fatally. When a dilute culture is painted on the mucous membrane of the nose carefully to avoid abrasion or dropped into the conjunctival sac, general infection, the pneumonic or the bubonic form, develops.

McCoy found that the ground-squirrel and the rock-squirrel of California are quite as susceptible as the rat. Strong and others in the study of the Manchurian outbreak, place the Siberian marmot in the same list. All these animals develop epidemics of the plague.

The guinea pig is slightly less susceptible than the above named animals to the plague bacillus on inoculation. No outbreak of the plague in the guinea pig in its native state is recorded, but there was an epidemic among these animals in the Zoological Garden at Sydney in 1902. Both gray and white mice are susceptible and may acquire the disease by feeding on infected material. Rabbits are somewhat less susceptible than guinea pigs and mice. They are killed by subcutaneous inoculations, but are not affected by feeding. Cats may acquire the disease through eating infected mice or rats. Hunter reports such cases from Hongkong. Ferrets, also used in destroying rats, may succumb when the feeding is long continued. Hyenas, jackals, and dogs are only slightly susceptible, especially by way of the mouth. According to Toyama, the Japanese bat is quite susceptible. Wilson reports an epidemic among hogs in Hongkong. Cattle, sheep, goats and horses are not susceptible. Subcutaneous inoculations in these animals are followed by local reactions, but general infection does not result. The testimony concerning the susceptibility of birds, reptiles, amphibians and fish is conflicting, but it seems to be safe to say that these animals play no part in the distribution of the disease.

In his early work, Yersin observed that an unusual number of the flies in his workroom died and later Nuttall showed that the fly may be infected, fatally to itself and may distribute the disease. The plague bacillus has been found in ticks, ants, and lice. The rôle played by the flea in this disease will be discussed later.

Apes resemble man in their susceptibility to plague, developing both the pneumonic and bubonic forms. Epidemics among these animals have been reported.

Modes of Infection.—According to Dieudonne and Otto, there are five geographical foci where the plague is endemic and from which it is

spread to diverse parts of the earth. Four of these are in Asia and one in Africa.

The first lies in the Kwen-fun mountains in the eastern Himalayas. From this place the plague extended in 1893 to Cochin China and Hong-kong. The second is in the southwestern foothills of the Himalayas. From this place the disease spread over India, reaching Bombay in 1896, and at the same time it traversed Persia and reached the Black Sea, invading Russia by way of Samarkand. This focus has a population of about 1,000,000, and English physicians have reported 30 smaller or larger epidemics in this region between 1823 and 1897. Many of

THE THIRD PANDEMIC OF PLAGUE EXTENSION OF THE DISEASE BETWEEN 1897 - 1917



Insects and Disease American Museum
of Natural History, Guide Leaflet No. 48

Fig. 51.

these resembled the black death of the middle ages and were certainly the pneumonic form of the plague. These epidemics affected both men and rats. Among the latter there exists a chronic plague which serves to keep the bacillus alive and virulent.

The third region is the most extensive, covering northern Mongolia and the Kirghiz Steppes. From this locality the plague in highly virulent form spread over Manchuria in the winter of 1910-1911. The infection of this region was first investigated in 1895 by two Russian physicians who discovered what has since been known as the "tarabagan" plague. The tarabagan or Siberian marmot is a small animal, widely distributed in the mountains about Lake Baikal and over the high tableland of western Siberia. It lives in large families in excavations

which they make and which are several feet deep. They leave their homes in great numbers in the fall in search for food. They are valuable on account of their fur and many of them, being ill with the plague, are easily captured. It has long been known that men become infected with a highly fatal disease in skinning the animals. The bacillus, having found a human host, is spread from man to man. The crowded life in small huts during the winter favors the spread of the infection. Whole communities are wiped out and in fear many flee to adjacent territory, carrying the disease with them. The marmots die in great numbers and are eaten by dogs and wolves. It is not known whether these animals are infected from such food or not. It is not supposed that they play an important rôle in the transmission to man. In man the pneumonic form of the plague is most in evidence, and the bacillus is disseminated by droplets in talking, sneezing, and coughing. The cervical glands are often involved, the inguinal less frequently. The fourth Asiatic focus lies in the mountains on the southwest coast of Arabia in the region of Assir on the Red Sea. This region has not been closely studied. The African nursery is found in Uganda near the source of the White Nile. It is supposed that this region is the breeding-place of the pestilence which has given Egypt an evil reputation for so many centuries.

The distribution from these centers and from secondary foci follows lines of traffic, penetrating distant lands and traversing the widest seas.

The infection in man may be transferred directly from one to the other. This is the chief method of spread in the pneumonic form. The sputum is full of the bacilli and in crowded families droplet infection is most common. Among the more civilized and the better housed peoples, this method of transmission is rapidly becoming less potent. In 1900 out of 276 cases in Sydney there were only ten houses in which more than one case developed. While "carriers" play an unimportant rôle in the transmission of the plague, it is known that those recovering from the pneumonic form may suffer from a more or less chronic bronchitis in which the sputum remains infective. The bubonic form does not favor direct transmission, but in this form the transfer may be indirect, by soiled clothing and infected houses. It has long been known that poverty and hunger favor the spread of this disease. Undoubtedly ignorance and filthy habits are also important factors. The figures from Bombay show the following distribution per 1,000,000 among the several classes: Low caste Hindoos, 53.7; Brahmins, 20.7; Mohammedans, 13.7; Eurasians, 6.1; Jews, 5.2; Parsees, 4.6; Europeans, 0.8.

The rat has long been suspected as playing a part in the distribution of this disease. In the great epidemics of the middle ages it was observed that rats come from their holes, lose all fear of man, become

uncertain in movement and die in great numbers. The most ignorant came to regard deaths among rats as foretelling the coming of the plague and fled from their homes when confronted with this evidence. The discovery of the bacillus and the study of its effects on the lower animals, as well as on man, has at least partially cleared up the mystery, although there are still unsolved problems. Rodents are the most active distributors of this disease. They carry the infection from house to house, from village to village, and from home ports to distant lands. The first appearance of the disease in a country previously free from the infection occurs in those occupied about the docks, receiving grain and other commodities from infected lands. Generally before a case has occurred in man the wharf rats are observed to behave peculiarly and then to die in large numbers. An infected rat has landed from the ship and has infected others. How does one rat infect others? The most probable answer to this question is that the sick new arrivals, one or more, have died and the natives have fed on the corpse and acquired the infection in this way. While a hungry rat may feed on the dead of its own species, it seems to prefer other food. Moreover, in a dead rat the bacilli of plague do not retain their virulence for many days, the exact time varying with the temperature. While a rat may be infected by feeding on a dead fellow, it is much more susceptible to inoculation through the skin. The conclusion is that while this method of transfer may and probably does occur, it is not the sole or even the most important method, and we shall look farther.

The urine and feces of the infected rat may be deposited on grain or other kinds of food and eaten by the native animal. This is a possibility easily submitted to experiment. It has been tried and has failed in all cases. Corn and other grains have been mixed with the urine and feces of infected rats and fed to sound ones with wholly negative results.

Rats serve as hosts to several parasites, among which is the rat-flea (*Xenopsylla cheopis*) and possibly this may serve in the transfer of the bacillus from one rat to another. In the first place this flea is taken from an infected rat, examined and found to contain the bacillus of plague. This seems to be a step in the right direction. Such a flea is crushed, a needle touched with the material is used to prick a healthy rat and this animal becomes infected and dies of the plague. Infected rats are kept in one side of a cage, uninfected ones in the other side. So long as the two are separated by a flea-proof partition the infection is not transmitted. Even when the partition is made of tangle-foot which catches the flea when it tries to pass to the other side, the sound rat remains sound. When such a partition is removed, the sound rat becomes infected. Rat-fleas are captured and fed on cultures of the

plague bacillus and then freed in a cage occupied by healthy rats which soon become infected. Infected rats are stripped of all their fleas and then placed in cages with healthy ones, which remain uninfected. Infected rats carrying their fleas are caged with guinea pigs, and the latter become infected.

These with many variations on the experiment have been made, and show conclusively that the plague is transferred from rat to rat or from rat to guinea pig by the bite of the rat-flea. This question is satisfactorily answered.

How is the plague transferred from rat to man? Evidently experiment along this line might be open to serious criticism and we must depend on observation, which is never so thoroughly convincing as experiment. Will the rat-flea bite man, and if it does will such a flea bearing the plague bacillus infect man? While we cannot use man in this experiment, we may employ his nearest relative, the ape. The rat-flea does bite the ape, and if the flea is infected with the plague bacillus its bite induces this disease in the ape. It is the testimony of several observers that uninfected rat-fleas, while preferring their own host, will in its absence feed on man.

Liston reports that in a certain house in India on April 6, 1904, many rats were found dead; on April 11, the house was so infested with fleas that the occupants sought sleep on the veranda. On April 17, two of these people were stricken with the plague. On April 20, 30 fleas were captured in this house and of these, 14 were rat-fleas, while of 246 fleas captured in uninfected houses, not one was a rat-flea. Tidswell, of Sydney, states that on a wharf where many rats were dead he was violently attacked by fleas.

It has happened that in some localities rats die of the plague, while there is no infection among men. This is explained by the absence of the flea, which, while widely distributed, is not found on all rats at all times. However, there is another factor which needs consideration. In the transmission of the plague from rats to man by the flea there is a time of variable length during which the flea is on neither rat nor man. The duration and conditions of this interval are widely variable and not equally favorable to the transmission of the disease. In a hot, dry climate rat-fleas soon die when detached from their hosts. Local conditions may play an important rôle in the transfer of the infected flea from rat to man.

An English Commission, studying the plague in India, summarizes as follows:

“The association of unusual humidity during the winter months in certain districts with severe epidemics of plague is so constant a phenomenon that we feel justified in concluding that one stands to the other as cause to effect. We have further good

grounds for believing that this cause exercises its effect mainly through its influence on the length of the life of rat-fleas when separated from their host, for the longer a rat-flea is able to survive in such circumstances the greater are its opportunities, in an infected area, for conveying the plague bacillus either to rats or human beings.”

Brooks, in a report on saturation deficiency and temperature on the course of epidemic plague, concludes that plague does not maintain itself in epidemic form when the temperature rises above 80° F. accompanied by a saturation deficiency of over .30 of an inch. Also that in the presence of a high saturation deficiency, even when the temperature has been considerably below 80° F., plague epidemics cease.

Anti-Plague Measures.—Nothing is better illustrative of the value, and we might say of the necessity, of preventive medicine in the eradication of disease than the history of the anti-plague measures which have been and are now in operation over the whole world. During the past five years rodent plague has been more widely distributed than ever before. In our own country human plague has appeared in our continental territory at Seattle, in California and at New Orleans, and in our island possessions in Porto Rico, Hawaii and the Philippines. During the same time human plague has appeared in Greece, Italy, Portugal, England, British East Africa, Senegal, Island of Mauritius, along the Pacific Coast of South America—especially in Peru and Ecuador, in Japan and China. During the same time it has been endemic in India and in Indo-China. During a few months in 1914 there were 8,794 cases, with 7,728 deaths, in the Dutch East Indies. It is safe to say that at the present time (1922) rodent plague exists in most all of these countries; and wherever this form of the disease does exist transmission to human beings is a possibility. In 1900 the disease was introduced into San Francisco. At first the local authorities attempted for commercial reasons to deny its existence. Fortunately, the U. S. Public Health Service officer stationed at San Francisco at that time, the late J. J. Kinyoun, could not be induced to pervert the truth. He claimed that the plague did exist in San Francisco, and this claim was substantiated by a commission of experts appointed by the Surgeon General of the U. S. Public Health Service to investigate the matter. Had not effective measures been promptly resorted to, it is more than probable that the entire United States would have been devastated by this disease as Europe was in the fourteenth century. With the knowledge that the rat is the principal distributor of this disease, prompt measures were put in operation. More than 1,000,000 rats were caught, studied, and destroyed in the City of San Francisco alone; however, the delay had allowed the disease to spread among the ground-squirrels in California. From July 1, 1913, to November, 1914, over 20,000,000 of these pests were destroyed. The total number of human lives sacrificed in the State of California as a

result of this infection is less than 200. New Orleans has been frequently threatened with this disease, and as late as October, 1919, a few cases of human plague were found in that city. As has been already stated, the rat is not the only rodent which carries parasites that may act as distributors of the plague bacillus. The rat, however, in this country at least, is the most dangerous animal because it comes into closer contact with man.

According to Creel, who wrote in 1913, the number of rats in the United States far exceeds that of the human population. The same authority estimated that at that time the cost of supporting rats in this country amounted to \$167,000,000 annually. It should be remarked that this is a pre-war estimate. The amount we are now paying for the food of these undesirable guests must be multiplied several times. The rat is wonderfully prolific. An ordinary female produces young six times yearly and supplies from six to twelve in each litter. A full-grown female has been known to make a contribution twelve times in one year. The rat is a precocious animal and begins to multiply her kind when only three months old. This pest goes about like a thief in the night and its depredations are not always attributed to the proper source. The rat must be exterminated. The slogan "no rats, no plague" is practically true; in this country at least. There are many ways employed in the eradication of the rat, the majority of which should be regarded as only of temporary value. Among these should be placed trapping and poisoning. Experience has shown that the snap trap is more valuable than the cage trap. To give some idea of the extent to which traps may be used it might be said that in the eradication of the plague in Porto Rico 9,000 traps were used, and in the capture of rats on ships 140 traps are needed on the average for each vessel. Experts are needed to trap rats. Rats are not altogether devoid of brain-cells and these they evidently use. It is difficult to induce a rat to enter a trap so long as there is abundance of food outside the trap. In a general way, cheese, toast, and bacon apparently are especially tempting to this rodent, but it is a foolish rat that will enter a trap so long as he finds lying about an abundance of palatable food. Taste in the rat is apparently a matter of habit and education the same as it is in man. That food upon which he has been in the habit of feeding is the one most likely to attract him. Trapping of rats is essential in order to secure them for examination, but at best it is an emergency method of deratting a locality.

The use of poison is not so satisfactory as trapping; however, it may be used as an adjunct. The dead rats cannot always be found and there is no way of measuring this method of extermination. The principal poisons used are phosphorus and arsenic. The former is mixed

with glucose to prevent spontaneous combustion and then worked into a pasty mass with lard or some other grease and spread upon bread. It is said that rats will not eat food which has been handled by man, and therefore, people who cut the bread should before doing so smear their hands with oil of aniseed.

According to Kitano, poisons have been used in Japan in the extermination of rats from very ancient times, and this author concludes that this is the most effective method employed in the extinction of these pests. He gives the following method for the preparation of his phosphorus poison:

“Place the given quantity of phosphorus in a double pan containing sesame oil, and, keeping it at 44° C. stir the contents well until all the phosphorus melts. Then stir in flour, being careful to keep up the temperature. If the compound gets too thick add more oil. Keep stirring, being careful to avoid lumps forming, until it is of a fit consistency to spread on bread. Take a piece of bread weighing 750 grams and cut into 400 pieces. These biscuits are placed in an earthenware vessel and the phosphorus compound poured in. The whole is then stirred so that the poison adheres evenly to every piece of bread. It is then transferred to a wooden vessel containing flour with which it is covered.”

In its importation from one country to another the plague is for the most part a ship-borne disease. Of course, rats may hide in freight boxes or in bundles and be transported by rail or by more primitive methods, but this method of importation is of small importance compared with that by sea. At present, ships from plague-infested countries are deratted by sulphur dioxid or cyanid gas. Creel, as a result of experiments made at New Orleans on more than 200 vessels, concludes that the last mentioned gas is the more efficient. However, the danger of human poisoning is increased and as a rule sulphur is used. When a ship from a plague-infested country reaches a port, the health officer instructs the captain where he is to bring his vessel to rest. The hawsers holding the ship in position are fitted with rat guards. It is true that rats may reach shore by swimming when the distance is not greater than half a mile, but whether a rat would voluntarily leave a ship and take to the water with the purpose of reaching land is a question. An English author states that he actually saw rats leaving vessels and swimming ashore in the waters of Bombay harbor. An expert goes aboard the ship furnished with a blue print of its structure. In the absence of these he must measure every compartment of the ship. Pots of sulphur are brought aboard and burned in the proportion of three pounds of sulphur to every 1,000 cubic feet of space. The efficiency of this method depends largely upon the construction of the ship and the nature and placement of its cargo. With old wooden ships it is almost impossible to reach the deep recesses of the hiding places with the gas in sufficient concentration to kill the rats. It is necessary not only that

the ship should fail to make contact with the dock, but with other ships as well. Rats have been known to transfer their passage from one ship to another and to proceed from an uninfected port to a distant one.

The examination of rats in order to ascertain whether they are infected with plague is not either an easy or a pleasant task. It may be interesting to state that from July 1 to November 1, 1914, 104,227 rats were examined at New Orleans. Of these 191 were found infected. The rats caught in the traps are brought to the laboratory, usually in bags. The rat is dipped in some solution which kills both the host and its guests, usually gasoline. The dead rats are combed for fleas and the number found on each animal noted. The rat is then fastened to a board and opened from chin to pubis. Whether the rat has plague or not may be determined by either macroscopic or microscopic methods. In 1906, an English Plague Commission in India decided that a microscopic examination is not necessary. Subcutaneous injection, pleural effusion, bubo and granular liver—any two of these conditions justify the diagnosis of plague infection. The Commission reports:

“The results of tests carried out for the purpose of comparison make it manifest that the naked eye is markedly superior to the microscopic method as an aid in diagnosis.”

Most experts agree in this finding. However, Williams points out that in the examination at New Orleans 35 per cent of the infections would have escaped detection had not the microscopic examination of smears been resorted to. In all cases of doubt, whether the examination has been macroscopic or microscopic, guinea pigs are inoculated. Most experts agree, Williams among them, that if either method is to be used singly the macroscopic is superior.

The only method of permanently eradicating the rat is to starve him and this means rat-proof construction for all buildings, including docks, warehouses, business houses, and residences. Letton in 1915 estimated that the cost of rat proofing of the more than four miles of docks at New Orleans would cost a little more than \$800,000. No doubt this seems like a large sum, but when we take into consideration the fact that the yearly cost of protecting New Orleans against the plague, principally devoted to the destruction of rats, is not less than half this sum, we can easily understand that the investment would be a good one. Apart from the eradication of the plague, the universal adoption of rat-proof buildings would save enough grain and food of various kinds to abundantly justify the increased primary cost. Fortunately, the use of cement in construction promises ultimately to eradicate the rat. Even rat proofing of buildings already constructed is an important factor in the eradication of the plague in communities into which the disease

has already been introduced, as was shown by the work done at San Juan, Porto Rico. Surely man's superior intelligence should enable him to get rid for all time of this undesirable guest.

Measures for Personal Protection.—For many years Haffkine's vaccine has been used in India. This consists of sterile broth cultures of *B. pestis*. The results are reported as favorable.

German vaccine is made by the sterilization at 65° C. of forty-eight hour agar cultures.

Yersin has prepared a serum by the immunization of horses with plague cultures. The sera are standardized by their protective power as measured in white rats. This is used in the treatment of the disease. There have been three cases of laboratory infection with *B. pestis*; two in Vienna and one in Ann Arbor. The two former died without treatment and the latter recovered after receiving large intravenous injections of Yersin's serum.

In working with the pneumonic plague, the American commission which dealt with this disease in Manchuria, found it necessary to wear masks. These consisted of heavy cotton flannel covering the entire head and provided with a window of sheet celloidin over the face.

While vaccination against this disease is undoubtedly of some protective value, it must never be allowed to supplant antiratic methods. It is also true that the use of the specific serum is of value in the treatment of the disease, but its worth has not been demonstrated in any epidemics.

Recent Outbreaks of Human Plague.—Since the World War, plague has appeared in many widely separated localities. We have already referred to the great epidemic in Manchuria in 1910-1911 when more than 60,000 deaths occurred. Immediately following that outbreak the Chinese Government took official steps to prevent a recurrence of the disease within its dominion. These measures seem to have been, on the whole, successful. While scattered cases have been reported now and then in various parts of Manchuria and northern China, there was no notable epidemic until 1918, when 20,000 persons died from this disease in Mongolia. In 1920 plague appeared in several localities in northern and northeastern China. The local authorities were able apparently to control these threatened epidemics. In 1921, 164 cases, with 108 deaths, were officially reported at Tampico, in Mexico. At the request of the Mexican Government, Michel, of the U. S. Public Health Service, was called to the aid of the Mexican authorities and the disease soon stamped out. During the summer and fall of 1920, 18 cases, with 12 deaths, were reported from Galveston, the last occurring November 13. Nearly 65,000 rats were captured in the campaign against this epidemic, 67 of which were found to be carriers of the bacillus. In 1921, 66 cases were reported in Paris, a few of which, however, proved not to be plague.

It was the belief of the physicians treating these cases that the specific antiserum was of marked value. Scattered cases have occurred in many other parts of the world and, as we have already stated, rodent plague has probably a wider distribution during the last three or four years than has been known in any previous period.

Writing recently (1921) Teh says:

“The vast empire of India with its 320,000,000 people may be considered permanently infected, although certain administrative areas like the Punjab, the Presidency of Bombay, and the United Provinces of Agra and Oudh suffer to a greater extent than the hilly Province of Assam where during the last six years only one case has been recorded. During the last 18 years, over 10,000,000 persons have died of the pest in India alone. In other parts of Asia frequent outbreaks of plague have occurred during recent years, e. g., Ceylon, Straits Settlements, Dutch East Indies, Siam, Indo-China, Japan, Hongkong, the Provinces of Kwangtung and Fukien (particularly at the ports of Canton, Swatow, Amoy, Foochow), Manchuria and Siberia. The coal mining center of Tongshan, three hours by rail from Tientsin, was infected by some bubonic cases from Hongkong in 1898 and lost 1,000 lives in four months. The port of Newchwang (Winkow) in South Manchuria was invaded in 1899 (probably again through vessels from the south) and lost in five months 2,000 people. From 1901 to 1903 isolated cases were detected, but they never resulted in an epidemic. It is strange that the great pulmonary epidemics of 1911 and 1921 did not touch either Tongshan or Winkow, although both lie on the main highway of railway traffic.”

It grows more and more evident that there are other factors in the spread of plague than the rat, bacillus, and man. Notwithstanding the presence of all three of these factors, some countries are never seriously invaded by a plague epidemic; in other words, certain localities are plague immune. A full and satisfactory explanation of this phenomenon has not been developed. Studies in India suggest that epidemic plague prevails only in countries in which the common condition is one of marked humidity in atmosphere. We suppose that temperature, dryness of atmosphere, and a possible intensity of sunlight are not favorable to the flea during the time which elapses between leaving his rat and finding his human host.

According to Harrison, of the Public Health Service, there were during 1907-1908 a total of 159 human cases in San Francisco, with 77 deaths. Since October, 1908, no plague infected rodent has been found in this city, with the single exception of one ground-squirrel shot in the Glen Park District in 1917. The outbreak in Oakland simultaneous with that in San Francisco (1907-1908) involved only 12 human cases, with 7 deaths. Since October, 1908, no plague infected rodent has been found in Oakland, but in 1919 and 1920 several infected squirrels were shot in the hills east of the city within the corporate limits.

“Following the disappearance of plague in man in the east bay cities in 1908 trapping operations were continued until April, 1914, since which date no operations have

been carried on with the exception of a short period of trapping following the explosive outbreak of August and September, 1919. This outbreak holds considerable interest in that it represents the only epidemic of pneumonic plague reported from the Western Hemisphere. The first case was unquestionably infected from a plague squirrel which was probably shot for food, the symptoms first indicating the bubonic type, pneumonia developing after incision of the bubo. After the development of pneumonia the infection was transmitted by direct contact to 12 additional cases, all of which terminated fatally. The abrupt subsidence of the infection was, no doubt, due to the hospitalization and isolation of cases together with the climatic conditions prevailing in August and September, which it is well known are not conducive to the spread of respiratory infections. At this time approximately 6,000 rats were trapped, none showing evidence of plague infection. It has not been possible to induce these cities to take the necessary measures to build out the rat, or provide for the continuous employment of a force of trappers in order that a check might be kept on the possibility of a recrudescence of the disease. In view of the close proximity of plague infected ground squirrels to the thickly inhabited east bay region, it is exceedingly unfortunate that more interest in the situation cannot be secured."

Harrison concludes his paper with the statement that an epidemic focus of plague infection now (1921) exists in California in the coastal range extending from the bay region southward approximately 200 miles. So long as this focus remains it is to be expected that an occasional case of human plague will develop in it.

McCoy states:

"Pneumonic plague in man, rarely occurs from rat infections, and it is an interesting and possibly significant fact that in plague squirrels there is a very definite tendency to pulmonary localization, a condition which never occurs in plague in rats."

Bibliography

- BROOKES, R.: A History of the Most Remarkable Pestilential Distemper, London, 1721.
 BROWNE, J.: A Practical Treatise of the Plague, etc., London, 1720.
 BULLEIN, W.: A Dialogue Against the Fever Pestilence, London, 1578.
 CANTLIE, J.: Plague: How to Recognize, Prevent, and Treat Plague, London, 1901.
 FALCONER, W.: An Essay on the Plague, Bath, 1801.
 FORBES, F.: Thesis on the Nature and History of Plague, Edinburgh, 1840.
 HAFFKINE, W. M.: Experiment on the Effect of Protective Inoculation in the Epidemic Plague of Bombay, 1898.
 HARRISON, W. T.: South. Calif. Pract., 1921, xxxvi, 53.
 HENDERSON, W.: A Few Observations on Plague, etc., London, 1689.
 HENDLEY, W.: Loimologia Saera, London, 1721.
 HIRD, W.: Remarks Upon Pestilence, etc., London, 1753.
 KENNEDY, P.: A Discourse on Pestilence, London, 1721.
 LODGE, A.: A Treatise of the Plague, etc., London, 1603.
 NANKIVELL, A. T.: Hospital & Health Review, n.s., 1921, i, 1.
 PARACELSUS, A. P. T.: Vom Ursprung der Pestilenz, Basel, 1575.
 PYE, G.: A Discourse of the Plague, etc., London, 1721.
 QUINCY, J.: An Essay of the Different Causes of Pestilential Disease, etc., London, 1721.
 RUCKER, W. C.: U. S. Pub. Health Reports, 1915.
 SIMPSON, W. J.: A Treatise on Plague, etc., Cambridge, 1905.
 TEH, WU LIEN: National Med. Jour. of China, 1921, vii, 177.
 THOMSON, G.: The Pest Anatomized, etc., London, 1616.
 WOODALL, J.: A Treatise on the Plague, etc., London, 1639.

CHAPTER XXXIII

TYPHUS FEVER

Spotted Typhus; Jail Fever; Ship Fever; Crowd Fever

Description.—This is an acute self-limited febrile disease, the virus of which has not as yet been positively identified. It terminates, as a rule, in recovery or death by the end of the second or third week. The fever is accompanied by a macular eruption, which usually develops about the seventh day and is most abundant over the trunk.

History.—Some medical historians are satisfied that they find evidence of the existence of typhus fever among the ancient Hebrews and their contemporaries, but this is a matter of conjecture. While this disease has long been known as *morbus pauperum* associated with want and hunger, we must not infer that it is the only fever which develops and thrives among the needy and in times of scarcity of food and other privations. Poverty, hunger, and overcrowding favor the development and distribution of many infections. In his book on epidemics, Hippocrates describes cases which are certainly suggestive of typhus fever. The following is the report of a case believed to have been typhus, as made by Hippocrates and as translated by Adams:

“In Thasus the wife of Dealees, who was lodged on the plain, from sorrow was seized with an acute fever, attended with chills. From first to last she wrapped herself up in her bedclothes; still silent, she fumbled, picked, bored, and gathered hairs (from the covers); tears and again laughter; no sleep; bowels irritable, but passed nothing. When directed, drank a little; urine thin and scanty; to the touch of the hand fever was slight; coldness of extremities. On the ninth (day) talked much incoherently, and again became composed and silent. On the fourteenth breathing rare, large at intervals; and again hurried respiration. On the sixteenth looseness of bowels from a stimulating clyster; afterwards she passed her drink nor could retain anything, for she was completely insensible; skin parched and tense. On the twentieth much talk and again became composed; loss of speech; respiration hurried. On the twenty-first she died. Her respiration throughout was rare and large. She was totally insensible; always wrapped up in her bedclothes, either much talk or complete silence throughout. Phrenitis.”

The great pestilence which devastated Athens and which was so well described by Thucydides, was either typhus or the pneumonic form of the plague. Medical historians differ on this point. Livy and Tacitus describe many epidemics in the classical period of Rome. Some of these were undoubtedly epidemics of the plague, while descriptions of others suggest typhus. During the dark ages medical science was so overshadow-

owed by credulity and superstition that the records of that time are of but little value. In the siege of Granada in 1489, no less than 17,000 of Ferdinand's soldiers died of fever, which was designated as "tabardillo" on account of the spots appearing on the skin. This term still remains one of the Spanish names for typhus fever. In the sixteenth century two Italian physicians, Fracastorus of Verona and Cardanus of Pavia, described typhus fever so plainly that there can be no doubt about the disease which then prevailed. In four years (1550-1554) it is said that more than 1,000,000 people in Tuscany were destroyed by typhus. Fracastorus describes the disease under the name "febris pestilens" and states that it was vulgarly known as "lenticulae" or "puncticulae." He states that from the fourth to the seventh day red eruptions appear on the arms, chest, and back. They resemble flea bites, only are somewhat larger. They also resemble lentils, and from this comes the popular name. The most marked symptoms mentioned are great prostration, feeble pulse, injected conjunctivae, and low muttering delirium. Some are somnolent, while others are excited and wakeful; while in still others these states alternate. The disease lasts from seven to fourteen days, rarely longer. The majority of those who were bled died and a supporting treatment was recommended as the best. Cardanus and other Italian physicians state that many of the practitioners of the time mistook this disease for measles, and Massa, of Venice, wrote on the distinctions between the eruptions of this disease and those of measles and smallpox. About the middle of the sixteenth century typhus was widely prevalent in France, and Coyttarus, of Poitiers, wrote a monograph on it under the title "De Febribus Purparatis," and somewhat later, Ambrose Paré, the distinguished surgeon, wrote of "febris pestilens," which was marked by eruptions resembling the bites of fleas or bedbugs.

Under the name "Morbus Hungaricus" typhus appeared in the Army of Maximilian II in Hungary in 1566, and soon spread over the greater part of Europe. Sennertus and others have left valuable descriptions of this epidemic. The skin was marked by flea-bite eruptions. Headache was intense and generally followed by delirium. In some, the tongue became swollen and black. Parotid abscesses developed and gangrene of the limbs occurred.

Under the title "Febris Maligna Puncticularis Seu Peticularis," Castro, of Verona (1580), described the symptoms. He reported the pulse slow and weak; the tongue dry and black; the face and eyes greatly congested; delirium, followed by stupor deepening into coma; parotid abscesses in some; the eruption appearing about the seventh day and the disease continuing from 14 to 20 days. Castro says that this disease was known to the French as "la pourpre," to the Italians as "petecchie," to the Spaniards as "tabardillo," and to the Germans as "fleckfieber."

During the sixteenth century typhus fever was so prevalent in the jails of England that it was known as jail fever, and it spread among court officers when prisoners were brought before them for trial. This happened repeatedly and gave to court sessions the designation of "black assizes." The first of these of which record is left occurred in Cambridge in the thirteenth year of the reign of Henry VIII (1522). The justices, bailiffs, gentlemen, and other persons in court were seized with a fever which proved fatal to many. The most notable report of "black assize" is that at Oxford in the twentieth year of the reign of Elizabeth (1577). The prisoner was Roland Jenks, a bookbinder and a Roman Catholic, who was charged with treason to the state and profanity of the Protestant religion. He was tried and sentenced to lose his ears. The trial was held at Oxford Castle, July 4. With him several other prisoners were brought into court during the course of the trial. The chronicle states that an "infectious damp of breath" spread throughout the room. "Above 600 sickened in one night; and the day after, the infectious air, being carried into the next village, sickened there more than 100 more." By the twelfth of August, 510 persons had perished. "The infection arose from the nasty and pestilential smell of the prisoners when they came out of the jail, two or three of whom had died a few days before the assize began." Among those who contracted the disease there was marked loss of appetite, headache, sleeplessness, loss of memory, deafness and delirium, so that the victims behaved like mad men. The Catholics saw in this the scourge of God for the unjust punishment of Roland Jenks, and the Protestants attributed it to the "diabolical machinations" of the Papists.

During the Thirty Years War (1619-1648) the greater part of central Europe was desolated by war accompanied by famine and pestilence. That typhus fever predominated in these epidemics is plainly shown by both medical and lay writers, and the ravages of this disease were portrayed in both prose and poetry.

In 1658, Morton states that England was one vast hospital filled with victims of a fever with "*maculae latae et rubicundae morbillis similes in toto corpore.*" The great plague of London (1665) was preceded, accompanied, and followed by typhus, and their writings show that some of the most eminent medical men of the time, notably Sydenham, frequently confounded the plague and typhus in the reports of their cases. Under the title "*Febris Petechialis Vera*" Hoffmann, of Halle (1700), gave an excellent account of typhus and pointed out its distinction from the plague, which he designated "*febris pestilens.*" The eighteenth century saw no abatement of the epidemics of typhus. This disease had long afflicted Ireland under the name of "Irish ague," but it was not until 1708 that permanent records of its ravages in this island were made. From that time on for more than a century and a half, Ireland was afflicted by one epi-

demic after another just as fast as new generations supplied the crops of susceptible material. The historian has no difficulty in showing that each exacerbation was coincident with a period of great want and poverty, but this was a chronic condition of the Emerald Isle. During this period the people were oppressed by their rulers, divided among themselves, and held in the grossest ignorance and fed on superstition. Most of those who had enough energy emigrated to foreign lands, thus impoverishing their native country of its best blood to such an extent that it has not yet wholly recovered. Indeed, the population of Ireland today is less than half of what it was before the period referred to.

An account of one epidemic of typhus in Ireland is much like all others. Nothing to eat but potatoes; and the adult would devour ten or more pounds of these tubers each day in the vain attempt to supply his body cells with the minimum amount of protein demanded. Driven by hunger to sell the cow, furniture, and even his clothing, the Irishman and his family huddled together in rags and filth, while vermin fed on their bodies and simultapeously inoculated them with typhus. Murchison says:

“In Dublin, the servants of the upper classes were not allowed potatoes, and bread was portioned out to them sparingly, few persons had more than a quarten loaf in the week. The poor pawned their clothes, and even their bedding for money to purchase food, and, as a natural consequence, it was common for several members of one family to sleep in the same bed.”

According to O’Connell, 80,000 Irish died in 1740-1741 of famine and spotted fever, and about one-fifth the population of Munster perished. Writing of the nineteenth century epidemic of typhus in Ireland, Murchison says:

“Extreme distress ensued. The four pound loaf was sold in Dublin in 1817 for 1s, 9d; and the poor throughout Ireland are described as wandering about the country, gathering nettles, wild mustard, and other weeds to satisfy the cravings of hunger. * * * The probable population of Ireland at this time was in round numbers, 6,000,000, and the number of sick was estimated at 737,000, or about one-eighth. In Dublin alone there were about 70,000 cases, making about one-third the inhabitants.”

Of the same epidemic Carleton wrote:

“People collected at the larger dairy farms waiting for the cattle to be blooded, so that they might take home some of the blood to eat and mix with a little oatmeal. The want of fuel caused the pot to be set aside, windows and crevices to be stopped, washing of clothes and persons to cease, and the inmates of a cabin to huddle together for warmth. This was far from the normal state of the cottages or even of the cabins, but cold and hunger made their inmates apathetic. Admitted later to the hospitals for fever, they were found bronzed with dirt, their hair full of vermin, and their ragged clothes so foul and rotten, that it was more economical to destroy them and replace them than to clean them.”

The roads were filled with infected vagrants and many a poor cottier not only divided what he had in alms, but by giving shelter to the wan-

derer introduced the infection into his humble home, while "the dogs of the gentry kept all beggars from their gates."

The last great Irish famine (1845-1848) was due to the prevalence of relapsing fever and scurvy, as well as typhus fever. This scourge was foreseen in the development of the potato blight and was mitigated somewhat by the repeal of the corn laws, and by a change in the navigation laws permitting the carrying of food supplies in other than British bottoms. At that time Ireland lived almost exclusively on milk and potatoes. Although it produced more than enough grain to feed itself, even in these years of the potato blight, most of this had to be sent to England to pay the rents. Years before, both Malthus and Cobbett had protested against a people trying to live so exclusively on potatoes. The former wrote as follows:

"When the common people of a country live principally on the dearest grain as they do in England, on wheat, they leave great resources in scarcity; and barley, oats, rye, and cheap soup and potatoes all present themselves as less expensive, yet at the same time wholesome means of nourishment, but when their habitual food is the lowest in the scale, they appear wholly without resource except in the bark of trees like the poor Swedes; and a great portion of them must necessarily be starved."

After this famine the Irish ceased to rely so largely on the potato. Emigration to this country and Canada greatly increased, and "the population has steadily declined and the well-being of the people steadily improved."

Before dismissing the subject of Irish epidemics we wish to add a quotation from Creighton, showing, that the case mortality in this disease is higher among the robust and well fed than among the weak and hungry:

"There appeared to be a scale of malignity in the fevers in an inverted order of the degree of misery. The most wretched had the mildest fever, the artisan class or cottagers had typhus fatal in the usual proportion, the classes living in comfort had typhus of a very fatal kind. This experience, however strange it may seem, was reported by medical observers everywhere with remarkable unanimity. One says that six or seven of the rich died in every ten, others say one in three. Forty-eight medical men died in 1847 in Munster, most of them from fever; in Cavan County seven medical men died from fever in twelve months and three more had a narrow escape of death; two of the three physicians sent by the Board of Health to the Coast of Connemara died of fever. Many Catholic priests died, as well as some of the established Church Clergy; and there were numerous fatalities of the resident gentry and among others who administered the relief. Yet a case of fever in a good home did not become a focus of contagion. The contagion came from direct contact with the crowds of starving poor, their clothes ragged and filthy, their bodies unwashed, and many of them suffering from dysentery. The greater fatality of fever among the richer classes (of course, with a much smaller number of cases) has been a commonplace in Ireland and is remarked by the best writers."

Creighton in his valuable "History of Epidemics in Britain" has shown many interesting facts concerning typhus in England during the eighteenth century. We will follow his facts but will draw our own conclusions.

During the 50 years from 1715 to 1765 England was most prosperous financially. Moneyed men built up great fortunes and the necessities of life were abundant and cheap. With two or three exceptions harvests were rich and grain was exported in great quantities. Historians state that under the first two Georges there was general prosperity. Even Adam Smith speaks of the "peculiarly happy circumstances of the country during the reign of George II (1726-1760)."

Lecky says:

"All the evidence we possess concurs in showing that during the first three-quarters of the century the position of the poor agricultural classes in England was singularly favorable. The price of wheat was both low and steady. Wages, if they advanced slowly, appeared to have commanded an increased proportion of the necessities of life, and there were all the signs of growing material well-being. It was noticed that wheat bread and that made of the finest flour, which at the beginning of the period had been confined to the upper and middle classes, had become before the close of it, over the greater part of England, the universal food, and the consumption of cheese and butter in proportion to the population in many districts almost trebled. Beef and mutton were eaten almost daily in the villages."

Johnson in describing the general prosperity of that time wrote:

"There every bush with nature's music rings,
There every breeze bears health upon its wings."

However, there were even at that time some who saw beneath the surface of an abundant prodigality. An economist, Rogers, points out that prosperity was all on the side of the ruling classes and the capitalists, while the laborers were in "irremediable poverty and without hope." Their wages were artificially fixed by the quarter sessions and they were "kept in a condition wherein existence could just be maintained."

Creighton writes:

"But the eighteenth century, even the most prosperous part of it, from the accession of George I to the beginning of the industrial revolution in the last quarter or third of it, was none the less a most unwholesome period in the history of England. The health of London was never worse than in those years, and the vital statistics of some other towns, such as Norwich, are little more satisfactory."

In 1782, White wrote of the fever in London:

"The annual deaths under the old regime exceeded by a good deal the annual births. In the seven years, 1728-1735, according to the figures in the parish registers; the burials from all causes were 3,488 and the baptisms 2,803, an annual excess of 98 deaths over the births in an estimated population of 10,800 (birth rate 37 per 1,000; death rate 46 per 1,000)."

Creighton says:

"The mean annual deaths were never higher in London, not even in plague times over a series of years, the fever deaths keeping pace with the mortality from all causes, and, in the great epidemic of typhus in 1741, making about a fourth part of the whole. The populace lived in a bad atmosphere, physical and moral."

It is stated that the consumption of alcohol in London at that time amounted to six gallons per head per annum. A duty of 20 shillings per gallon did not prevent the poor from getting it, and large quantities of gin were smuggled in from Holland. In 1726 the College of Physicians presented this matter to the House of Commons with the following statement:

“We have with concern observed for some years past the fatal effects of the frequent use of several sorts of distilled spirituous liquor among great numbers of both sexes, rendering them diseased, not fit for business, poor, a burthen to themselves and neighbors, and too often the cause of weak, feeble, and distempered children, who must be, instead of an advantage and strength, a charge to their country.”

The poor in London were crowded into small quarters. In 1737 one house was found to contain 11 married couples and 15 single persons. A tax was levied on each window in a house and each window in cellar, stairway, and outhouse was counted and skylight included. “No window or light shall be deemed to be stopped up unless such window or light shall be stopped up effectually with stone or brick or plaster on lath.”

Debtors were thrown into prison, where some remained for years, and if they had any comforts while in prison they had to pay for them. Jailers grew rich out of the necessities of their wards. Those unable to pay were crowded into unbelievably small quarters. The first commission to inquire into these abuses reported:

“George’s ward, sixteen feet by fourteen and about eight feet high, had never less than 32 in it all last year and sometimes 40; there was no room for all to lie down, one-half the number sleeping over the others in hammocks. They were locked in from 9 P. M. to 5 A. M. in summer, longer in winter, and as they were forced to ease nature within the room, the stench was noisome beyond expression.”

It is a matter of common knowledge that the work of prison reform in England at the time of which we write was due largely to the efforts of John Howard, whose work was begun in 1773.

While the great land owners accumulated wealth, the poacher who snared a rabbit was sent to jail or deported. The condition of the poor was hopeless and much of the best blood of England flowed, willingly or unwillingly, into the United States, Canada, and Australia. However, typhus often pursued the poor emigrant in his flight by sea, and it is said that one-third the immigrants to America in the eighteenth century died during or soon after the voyage. It is well known that the fatality from ship fever continued through the early part of the nineteenth century. During the Revolutionary War (1774-1780) the number of British seamen raised was 175,990; the number of those who died of disease was 18,545, and the number of killed was 1,243.

Turner (Ireland and England in the Past and at Present, 1919) de-

scribes the flight from Ireland, stricken as it was by famine and pestilence:

“From the stricken land Irishmen began to flee in a mighty exodus which drained the island of its people. In 1841 the population had been 8,175,124; ten years later it was 6,552,385. In the decade (1851-1860) it is said that a million and a half Irishmen emigrated, fleeing from the old home to a new and greater Ireland, going most of them to the United States of America. These were the days of the ‘coffin ships,’ and of great prosperity for some of the shipping companies. Facilities were inadequate for the vast host of fugitives who crossed the Atlantic. In the days when negro slaves were brought from Africa to Liverpool or Jamaica, the anti-slavery societies used to exhibit a broadside showing a slaver, like a great floating coffin, with the bodies of slaves packed between decks as close as they could be put, there to stay in heat and thirst, in sickness and foul air, for all the long weeks while the passage was made. With the worst of the Irish emigrant ships now it was not very much better. Once Sir Robert Peel quoted the account of a man who had made the passage and had seen hundreds of people, men, women and children, huddled together indiscriminately, without light, with insufficient air, wallowing in filth, sick in body and heart, scarcely able to move, some raving in madness, some in the throes of death, dying without consolation, buried in the deep as the ship passed on. And those who survived and found in America the opportunities denied them in Ireland, who toiled to send back money to the aged and stricken not able to come, who presently rose up to power and prosperity in their new homes, most of them carried through their lives a hatred, often ignorant and unreasoning, but unquenchable and fierce, not able to see atonement or excuse, not able to forget or forgive, until, after generations had passed, in their descendants it might slowly burn itself away.”

It is interesting to note that during the eighteenth century English physicians for the most part were not much concerned with the poor and many of them saw but little typhus, while colleagues, busy among the poor, saw much of it. A Dr. Moss, writing of the disease in Liverpool, stated that typhus was rare, while at the same time and in the same city a Dr. Currie was seeing more than 3000 cases a year. In 1790 Liverpool was the second city in England, with a population of 56,000, while that of London was estimated at 800,000. According to Currie, 7,000 of the people of Liverpool lived in cellars and 9,000 more in back houses with small courts and with narrow passages into the streets. In ten years (1787-1796) 31,243 cases of typhus were registered, an average of 3,124 per year. In the last quarter of the eighteenth century Chester was regarded as the most desirable residence city in the kingdom. Within the walls, it had a population of about 3,500 and from 1764 to 1773 the death rate was only 17.2 per 1,000, but the poor lived outside the walls and Haygarth describes the condition as follows:

“The houses were small, close, crowded and dirty, ill supplied with water, undrained, and built on ground that received the sewage from within the walls. The people were ill-fed and they seldom changed or washed their clothes; when they went abroad they were noisome and offensive to the smell. * * * In these poor habita-

tions when one person was seized with the fever, others of the same family are generally affected with the same fever in a greater or lesser degree."

The second half of the eighteenth century saw the great manufacturing development of England due to the employment of machinery. During this time the poor were exploited by the manufacturer. The houses occupied by the operatives are said by Ferrier to have been dirty, without ventilation, and with the beds almost touching. "As soon as one poor creature dies or is driven out of his cell he is replaced by another, generally from the country, who soon finds in his turn the consequence of breathing infected air."

Practically the only voices heard in behalf of the poor were those of medical men, and in Manchester, Ferrier pleaded for them in strong language, from which the following quotation is made:

"I have seen patients in agonies of despair on finding themselves overwhelmed with filth and abandoned by every one who could do them any service. * * * The situation of the poor at present is extremely dangerous, and often destructive to the middle and higher ranks of society. * * * The poor are indeed the first sufferers, but the mischief does not always rest with them. By secret avenues it reaches the most opulent and severely revenges their neglect or insensibility to the wretchedness surrounding them."

It was the fact that typhus occasionally found its way into the midst of the rich, and, when it did, killed so many and so quickly that they were compelled to recognize that the misfortunes of the poor were of concern to themselves. Finally, in a half-hearted way, urged by physicians, growling about the wastefulness and improvidence of the laboring classes and driven by the occasional deadly outbreaks in their ranks, the ruling classes began to provide special hospitals for the isolation and care of cases of typhus. The London Fever Hospital was established in 1802.

The epidemiologic history of Britain during the Napoleonic wars presents many points of interest. Food prices were high. For a time American markets were closed to British manufacturers. Still, the period (1803-1816) was comparatively free from typhus, so far as Britain was concerned. In peace the poor man's business is to serve the rich, clothe himself in rags, rear his family in a sty and eat nothing. In war he becomes a hero, the defender of his king and country. He is well clothed, well fed, and all that is asked of him is that he die for his country, if need be. The wife and children at home must be cared for because the man at the front must be contented and more soldiers will be needed.

Immediately after the declaration of peace (1816) typhus began to increase and within another year it took on epidemic proportions. The condition of the London slums of that time is shown by a Parliament report quoted by Creighton:

"Calmel's Buildings, a small court near Portman Square, consisting of 24 houses,

in which lived 700 Irish in distress and profligacy, neglected by the parish and shunned by every one from fear of contagion. George Yard, Whitechapel, consisting of 40 houses in which lived 2,000 persons in a similar state of wretchedness."

In 1831 typhus became epidemic in England and continued its ravages for more than ten years. The destitution and sickness among the poor of Manchester in the latter part of this epidemic (1839-1841) furnished the basis of the story of "Mary Barton" written by Mrs. Gaskell. The author dwells on the bitterness on the part of the poor.

"The most deplorable and enduring evil which arose out of the period of commercial depression to which I refer, was this feeling of alienation between the different classes of society. It is so impossible to describe, or even faintly to picture, the state of distress which prevailed in the town at that time, that I will not attempt it; yet, I think again that surely in a Christian land, it was not known so feebly as words could tell it, or the more fortunate and happy would have thronged with their sympathy and aid. In many instances the sufferers wept first and then cursed. Their vindictive feelings exhibited themselves in rabid politics. And when I heard, as I have heard, of the suffering and privations of the poor, of provision shops where ha'porths of tea, sugar, butter, and even flour were sold to accommodate the indigent—of parents sitting in their clothes by the fireside during the whole night for seven weeks together—in order that their only bed and bedding might be reserved for the use of their large family—of others sleeping upon the cold hearth-stone for weeks in succession without adequate means of providing themselves with food or fuel—and this in the depth of winter—of others being compelled to fast for days together, uncheered by any hope of better fortune, living, moreover, or rather starving in a crowded garret or damp cellar, and gradually sinking under the pressure of want and despair into a premature grave; and when this has been confirmed by the evidence of their careworn looks, their excited feelings, and their desolated homes—can I wonder that many of them in such times of misery, and destitution, spoke and acted with ferocious precipitation?"

In 1847-1848 there was a revival of typhus in England under the name of "Irish Fever." The last epidemic in England occurred in 1863-1864 and was in part due to the "cotton famine" resulting from the civil war in our own country. Since that time typhus fever has gradually decreased in Britain, and has not, notwithstanding the World War, regained a foothold in that country.

From the fact that we have dwelt on typhus in Britain it must not be inferred that it was unknown or was less prevalent on the continent of Europe during the seventeenth, eighteenth, and nineteenth centuries. Indeed, it was constantly present and assumed epidemic proportions of varying intensity in divers places at different times. No European nation has been wholly free from it, and it has continued up to the present time to develop epidemics, especially in the Balkan States, Austria, and Russia. The World War gave most favorable opportunity for the development and spread of this disease, but thanks to scientific medicine it has not become a world scourge.

Taking Europe as a whole, the period from about 1670 to about 1850

may be considered as the typhus age. This does not mean that this disease did not exist before this period or that it had ceased with the close of it. Neither assumption would be true, but before that time typhus was overshadowed for many centuries by the more deadly plague. Still, it is a question whether, even at that time, typhus did not kill more than the plague. The former was constantly present, while the latter lapsed from time to time, apparently on account of lack of susceptible material. Even during the typhus age, other deadly infections, as smallpox, tuberculosis, diphtheria, etc., aided in rolling up heavy mortality lists. A complete history of typhus would be a valuable contribution to human knowledge and should be studied by statesmen and all interested in the welfare of the race, as well as by physicians. There is certainly one great lesson which it teaches, and that is, that the health conditions of the poor are of interest to all. No nation can be great so long as its laboring classes live under unhygienic conditions. Typhus impoverished Europe, not only by its high mortality, but by the great emigration from its shores, leaving the more or less degenerate to beget its future generations.

Before leaving the history of typhus in Europe, we wish to quote the definition of the disease given by the greatest English authority of the nineteenth century, Murchison:

“A disease attacking persons of all ages, generated by contagion or by overcrowding of human beings, with deficient ventilation, and prevailing in epidemic form, in periods or under circumstances of famine and destitution. Its symptoms are: more or less sudden invasions marked by rigors or chilliness; frequent, compressible pulse; tongue furred and ultimately dry and brown; bowels, in most cases constipated; skin warm and dry; a rubeoloid rash appearing between the fourth and seventh days, the spots never appearing in successive crops, at first slightly elevated, and disappearing under pressure, but, after the second day, persistent, and often becoming converted into true petechiae; great and early prostration, heavy flushed countenance; injected conjunctivae; watchfulness and obtuseness of the mental faculties, followed at the end of the first week by delirium, which is sometimes acute and noisy, but often low and wandering; tendency to stupor and coma, tremors, subsultus, and involuntary evacuations, with contracted pupils. Duration of the fever from ten to twenty-one days, usually fourteen. In the dead body no specific lesions; but hyperemia of all the internal organs, softening of the heart, hypostatic congestion of the lungs, atrophy of the brain and edema of the pia mater are common.”

Typhus fever became epidemic in Mexico soon after the conquest (1530), and has continued in endemic form, with occasional severe exacerbations, to the present time. According to Liceaga, the second recorded epidemic occurred in 1545 and the third in 1575. In 1736-1737, the disease is said to have killed 192,000. During the nineteenth century there were many exacerbations, the most extensive of which was in 1861. At the present time typhus is endemic in Mexico, where it is still known under the old

Spanish name of "tabardillo." In December 1915, 11,000 cases of typhus were reported in the City of Mexico and its suburbs.

During the World War there was but little typhus in the armies of Britain, France, Italy, the United States, and Germany; more in the armies of Russia and Austria. A great epidemic introduced by Austrian prisoners spread through Serbia early in 1915. In April of that year it was estimated that the deaths reached 9,000 per day, and it is stated that during the year more than 150,000 people died of this disease. The epidemic extended into Bulgaria and Roumania. In the early summer of 1915 an American Red Cross Expedition visited these countries and succeeded, with the aid of the oncoming hot weather, in checking the epidemic.

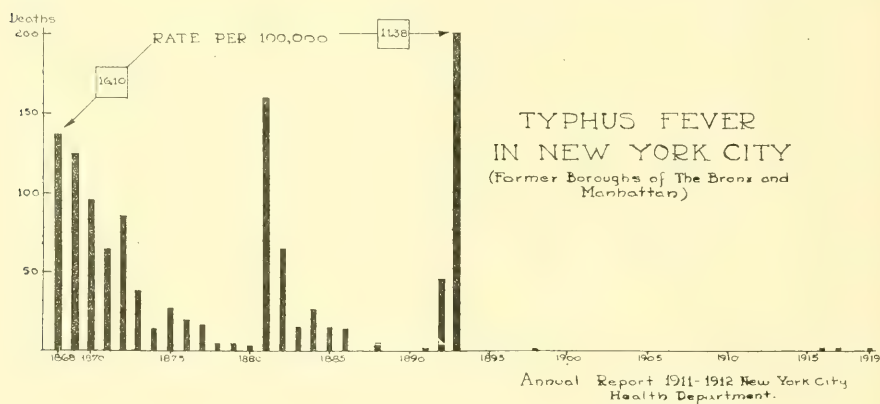


Fig. 52.

In the United States typhus fever has never reached serious epidemic proportions. During the first half of the nineteenth century it was occasionally found in jails and penitentiaries. A small outbreak was observed in Philadelphia in 1883 and another in New York in 1891-1892. A few cases have been reported from time to time among recently arrived emigrants from Europe.

TABLE XXXVI

1900	5	1910	2
1901	0	1911	5
1902	7	1912	6
1903	1	1913	8
1904	2	1914	3
1905	3	1915	2
1906	0	1916	35
1907	2	1917	16
1908	0	1918	3
1909	3	1919	6

From 1900 to 1919 inclusive the records show a total of 109 deaths from typhus in the registration area. The deaths by years are shown in Table XXXVI.

Of the 35 deaths in 1916, 26 occurred in Texas, 1 in California, 4 in Colorado, 2 in Missouri, 1 in New York and 1 in North Carolina. In 1917, 11 of the 16 deaths occurred in Texas, 3 in New York, 1 in Massachusetts and 1 in North Carolina.

From 1898 to 1911 Brill, of New York, collected and reported upon several hundred cases of acute fever which he distinguished from typhus fever, and described as follows:

“An acute infectious disease of unknown origin and unknown pathology, characterized by an incubation period of from four to five days, a period of continuous fever, accompanied by intense headache, apathy, and prostration, profuse and extensive erythematous maculo-papular eruption, all of about two weeks’ duration, whereupon the fever abruptly ceases either by crisis within a few hours or by rapid lysis within three days.”

For some years this was known as Brill’s disease, but later it was shown by Anderson and Goldberger to be typhus fever. Importations of this disease by immigrants into this country have been constant and it is probable that at no time have our large cities been wholly free from it, but in most instances it has been limited to recently arrived immigrants and those directly in contact with them. Doty says: “Out of 439 cases of typhus fever which occurred in New York during 1892-1893, 434 were removed from the poorer tenement and lodging houses, principally the latter.”

In the records of the Civil War, 1723 cases with 572 deaths are reported under this name, but the diagnosis of many of these was questioned by the best medical officers, such as Woodward and Clymer. No cases were reported by Confederate officers. It is certain that typhus did not play any marked part in the mortality of that war, although body lice under the name of “gray-backs” were carried frequently by soldiers. Evidently the lice did not carry the specific infection.

Typhus fever has always been widely prevalent among the poor people of Russia and Poland. According to the Health Committee of the League of Nations, there were during the years 1919-1920, 20,000 cases of this disease in that country. Beginning in 1918 there was an enormous rise in the incidence of this disease, and while there is no part of Russia that has entirely escaped, the epidemic has been most marked along the Volga.

During the World War, among the troops of this country there were 7 admissions for typhus in 1917 with no deaths, 11 admissions in 1918 with 2 deaths, and no admissions or deaths in 1919. Considering the thousands of cases in parts of Europe at the time, it is most remarkable that an army in active campaign could escape with so few cases.

In 1909, Nicolle, a French army surgeon stationed in Algiers, made notable discoveries concerning the transmission of typhus fever. In the first place, he induced the disease in the chimpanzee by injecting the blood of patients and in like manner he transferred the disease from the chimpanzee to the macacus monkey. He was not able to transfer the disease in this way directly from man to monkey, but could do so indirectly through the chimpanzee. He concluded from this that the virus is in-

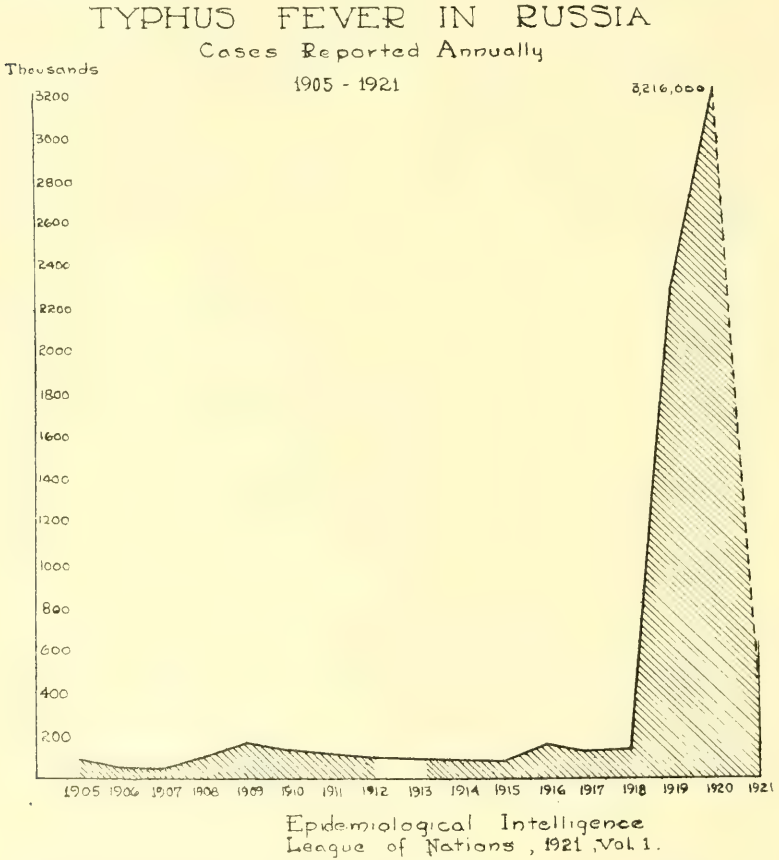


Fig. 53.

creased in intensity by passage through the chimpanzee; furthermore, Nicolle succeeded in transmitting typhus from monkey to monkey by the bite of the body-louse (*pediculus vestimenti*). Typical eruptions were secured in the chimpanzee constantly, but not uniformly in the monkey. The fact that typhus is transferable from man to man, from man to monkey, and from monkey to monkey, by the body-louse has been confirmed by the researches of Anderson and Goldberger, Ricketts and others. In the study of the transmission of typhus more than one medical man

has contracted the disease, and of six American physicians who carried on these studies in Mexico three became ill and two died—Conneff, of the State University of Ohio, and Ricketts, of Chicago. These are names now added to the martyr roll of science.

From time to time in the past, both before the World War and since, typhus fever has occasionally filtered into the United States. The sources from which this disease has come have been Europe and Mexico. From Europe the bearers of this infection have been immigrants, and it is probable that New York has seldom been entirely free from this disease. There was quite an epidemic in that city in 1867 and 1868. From the last named date until 1881, secondary cases were not reported in New York. In 1881 there were 811 cases with 225 deaths in New York and 11 cases with four deaths in Brooklyn. In 1883 there was a small epidemic in Philadelphia. From time to time, an American mining expert or some other prospector has acquired the disease in Mexico, but, so far as we have learned, there have been no secondary cases in this country due to the acquisition of this infection by American visitors of this class to Mexico. From time to time Mexican laborers, especially those engaged in work on the railroads, have brought the disease into this country. The most interesting report upon an epidemic of this kind is that made by Boyd of an outbreak at Ft. Madison, Ia., in 1916. In the small railroad hospital at this place there were eight cases, including the physician and three nurses in the hospital. Boyd handled this outbreak in a masterly way and the Santa Fe Railroad, under his direction, put into operation four disinfecting trains, which apparently completely eradicated the disease along its lines. Boyd makes the following statement concerning the method he employed in doing this work:

“The contemplated campaign of louse extermination among this Mexican population considered three things, (1) the delousing of the persons in the Mexicans themselves; (2) the delousing of their clothing, bedding and other intimate personal effects, and (3) the delousing of their bunks in the cars occupied by them. Since the necessity for this work existed at other points along the road than Iowa, the magnitude of the task was greatly increased. It appeared therefore that some portable equipment and system of operation must be devised which could be taken from place to place to accomplish this purpose. Time was pressing and the equipment must be such that it could be immediately constructed from materials on hand in the railroad shops and from such supplies as could be drawn from those on hand in the railroad store house and with the help of the regular railroad employes. It was decided to accomplish the delousing of the Mexicans themselves by a ten minute bath in kerosene and soap suds, with a kerosene and vinegar bath for the hair. Clothing, bedding, etc., was deloused by exposure to a temperature in excess of 160° F. for twenty minutes. The sleeping quarters in the bunk cars were deloused by spraying with kerosene. Dry heat was considered preferable for the destruction of lice and eggs in the clothing, as it could then be immediately returned to the men, hence saving time. Fumigation of the bunk cars did not seem practical, owing to their loose construction and the length of time

taken by such a process. At my suggestion the Santa Fe undertook to prepare a train for the convenient delousing of the Mexicans along their line, its construction and equipment being according to my directions. This train consisted of four cars. The first was a freight car in which was constructed an oven heated by steam coils, in which clothing and bedding could be subjected to a dry heat in excess of 160° F. for the destruction of lice and nits. Storage space for supplies was provided in this car. Two heated bath cars, in which the Mexicans could be bathed in kerosene and soap suds were next in the train and a way car was also provided for the disinfecting crew of five Mexicans.''

Pediculus Vestimenti (Also Known as P. Humanus and P. Corporis).

—Since it has been demonstrated that this parasite is the distributor of so serious a disease as typhus fever it has become the object of numerous studies. Among the first to report upon the habits of this louse was Shipley, of England. According to him, the body-louse is somewhat larger than the head-louse and carries longer antennae. The male is about 3 mm. long and 1 mm. broad. The female is about one-tenth larger. The color of the louse is said to vary with that of the people on whom it feeds, black, brown, and with different shades of grayish white. It does not move about over the surface of the body but is always attached to the inner side of the underclothing. Even in feeding it remains attached to the clothing by at least one of its six legs. It often happens that when a lousy person is stripped, no lice can be found on him, but the inner side of the underclothing may be alive with them. When grown for the purpose of study, they must be permitted to attach themselves to bits of flannel and these must be brought into contact with the skin and the lice allowed to feed twice daily. They take hold promptly and feed greedily, but never detach themselves from the flannel. The female after pairing begins to deposit eggs or nits at the rate of about five per day. These hatch after periods which vary markedly with the temperature. Cold delays hatching, but even freezing does not destroy the nits. Under favorable conditions the larvae emerge about the sixth day and immediately begin to feed. Body-lice do not seem to be hardy and soon die unless they have frequent opportunity of feeding, but the clothing may carry nits quite indefinitely, and these may hatch when conditions become favorable. The newly hatched do not survive more than 36 hours without food.

The optimum temperature for the activity of this parasite, including the laying and hatching of eggs, is about 95° F., slightly below that of the human body and about the temperature ordinarily maintained at the surface of the body. At this temperature copulation takes place every two or three days and a single copulation suffices to fertilize all the eggs laid during the following 20 days. No eggs are produced at temperatures below 77° F. and the daily exposure, even for a few hours, to a temperature of 60° F. results in a marked falling off in egg production. At temperatures above 95° F., especially when accompanied by increased humid-

ity, the life of the parasite becomes precarious and the production of eggs ceases. Either complete drying or excessive humidity retards all the functions of this parasite. This accounts for the fact that typhus fever is not found in certain hot countries and disappears with the advent of the hot season in temperate regions. The eggs of the body-louse are about 1 mm. in length and are glued to the fibers of the clothing, especially along the seams. Other lice deposit their eggs on hair. The body-louse will do so when there is no other object to which she can attach the eggs, but in doing so she shows less skill in her workmanship. The lice show a nesting tendency and deposit their eggs in clusters often numbering 50 or more. Newly hatched lice are ready to function as soon as they emerge from the egg and die within 24 to 48 hours when deprived of food. At a temperature of 95° F. the young pass their first molt in three days, the second in five or six days, and the third which brings them to adult life, in eight or nine days; however, the rate of development is influenced markedly, as has been indicated, by humidity and temperature. The first copulation occurs within less than 12 hours after the last molt and the production of eggs closely follows. The length of life of individuals is placed at between 35 and 40 days.

According to Bacott, body-lice do not wander over the skin. They pierce the tissue and apparently rely upon their salivary secretion to dilate the capillaries, which gives an accumulation of blood upon which they feed. The time occupied in feeding varies from a few minutes to an hour or more. The louse pumps in the blood intermittently, resting for a while without withdrawing his lancet. It seems that the human body-louse cannot draw blood from the lower animals, while the dog-louse fails to feed through the human skin. The lice slowly digest the absorbed blood, depositing the waste material in their excreta, and apparently they prefer two meals a day. Lice that have been held in captivity until partially starved are apparently still able to pierce the skin, but, possibly on account of some deterioration in their salivary secretion, they are unsuccessful in drawing blood.

An important question concerns the possibility of the body-louse feeding upon other insects or dead material. According to Hall, a female body-louse taken from a Mexican baby was placed in a bottle with a head-louse taken from the same baby, when the former promptly devoured the latter. For three days the body-louse was given two head lice for its food. Later it was seen to eat crab-lice, small black ants, bedbugs, and even raw beef. When given a choice of the above mentioned dishes, head-lice were first eaten; then followed the bedbugs and the beef. These reports need confirmation, and are of importance because Hall claims that body-lice have been found in empty box cars used to transport Mexican troops weeks before, and he points out that

a ear thus infected with typhus would be a source of danger for a longer period than the few days that a louse can live without food. The bites of uninfected lice cause red pimples which itch, and scratching produces characteristic white scars surrounded by brown pigment. In this way large areas of skin may take on a mottled bronze color. It is said that the people of Russian Poland have always possessed, or have acquired, an insensibility to the bites of lice. It follows that among these people the louse ceases to be a disturber of the peace, but continues to act as a distributor of disease.

According to Anderson and Goldberger the head-louse (*pediculus capitis*) may also transmit typhus fever. This pest is smaller than its cousin, the body-louse, has only seven instead of eight abdominal segments, and the abdomen is hairy instead of naked. It wanders over all parts of the body but makes its home in the hair of the head, where it deposits its eggs, especially above the ears. Its eggs are smaller and only one can be matured in the louse's body at a time, but eight or ten may be laid in a day. The nits are glued to the lower end of the hair, generally in nests plainly visible to the unaided eye. The eggs hatch in ten or twelve days and reach maturity after two or three weeks, when they are again ready to reproduce. Chandler says:

“At this rate of reproduction, allowing only a 50 per cent hatch, a single pair of lice, theoretically, could produce over three-quarters of a million offspring in the fourth generation and in the course of less than three months.”

It is stated that the two varieties may interbreed.

The crab-louse (*phthirus pubis*) is a wholly different species from the two already mentioned. It has a broad short body with long clawed legs, presenting the appearance of a tiny crab, thus it derives its name. It infests the hairs of the pubic region and other parts of the body where the hair is coarse, and has been found in the armpits and in the beard. It is said that this louse is confined to the Caucasian race, but the writers know this not to be true, inasmuch as one of them has seen these lice on negroes and Japanese. The female crab-louse produces from 10 to 15 eggs and glues them one at a time to the hairs among which she lives. Hatching occurs in from six to seven days and the young become sexually mature in about two weeks. It is said that the eggs do not develop except at temperatures between 68° and 86° F., which are approximately the temperatures to which the eggs attached to the hairs beneath the clothing are exposed. This louse is not known to transmit any infection.

It should be noted that the louse is responsible for the transmission not only of typhus, but also trench fever and relapsing fever.

Delousing.—It is evident that the surest way to eradicate typhus

fever is to exterminate the human louse, and while we are at it, the extermination should include all varieties and species of this pest. The "cootie," as the body-louse was familiarly known to the millions of allied soldiers who served as his host, is quickly and effectively destroyed by steam. The soldier in the trenches could not, however, send his clothes to the steam laundry every time they became infested. Hundreds of experiments were made in laboratories in the search for some chemical agent which, when sprinkled on the underclothing, would prove sufficiently obnoxious to this uninvited guest and lead him to make a speedy departure. Such a preparation, in addition to its insecticide properties, must not irritate unduly the skin of the man within the clothes. The British used a preparation known in the army as N. C. I., consisting of naphthalene, 96 per cent; creosote, 2 per cent; iodoform, 2 per cent. This material was undoubtedly of some value. Naphthalene retains its killing power, when cloth is impregnated with it, for about 12 hours, according to the experiments of Moore and Hirschfelder. Many other preparations continue to be poisonous to the parasite for a much longer time, but most, if not all, of them proved too irritating to be of practical value. The French used two soaps, one containing 35 per cent cresol and 65 per cent naphtha, while the other contained 35 per cent xylol and 65 per cent naphtha. In all the allied armies as soon as soldiers were temporarily released from the trenches they proceeded to the rear, where their clothes were disinfected by steam. Our own army officers have taken every possible precaution to prevent the importation of lice into this country. It must not be understood from this that our soldiers were 100 per cent free from this pest when they were mobilized. Cases of louse infestation were found in nearly every camp in this country and in some the percentage was astonishingly high. This was especially true of draft men from the tenement districts of our great cities and among negro soldiers from the South. Delousing plants were in operation at embarkation ports in Europe and at debarkation ports in this country on the return of our soldiers. These plants consisted of large separate buildings. They were so arranged that more than 200 soldiers with all their clothing and equipment could be deloused in an hour. The procedure was provided for by Plotz and others who had had experience in the campaigns against typhus fever in the Balkans. The soldier entered the building with his barrack bag containing all his clothing. Leather materials, rubber and celluloid articles, and money were deposited in lockers. The man received two tags bearing the number of the locker and then proceeded to the disrobing room with his barrack bag. All his clothing was placed in this bag, which was tied and numbered with one of the tags, the man retaining the other. The bag was then placed, with others, on a carriage and pushed into a

steam sterilizer, which was $18\frac{1}{2}$ feet long by 5 feet in diameter and provided with two cars and transfer tracks so that one car was being loaded or unloaded while the other was in the sterilizer. The soldier then proceeded to the hair-cutting room, but before entering he was inspected for vermin and nits. If these were found, the hair of the head, of the axillary and pubic regions was clipped with an electric hair-cutting machine. In infested cases the axillary and pubic regions were shaved. From the barber shop the soldier entered a shower room where a bath with liquid soap and warm water was obtained. The soap used contained kerosene. The man, thus thoroughly clean, went to a drying room where he was provided with clean towels. In the delousing stations, plans were made for pressing rooms where wrinkled clothing could be put in shape. Two toilets were provided, one for dirty and one for clean men. All attendants in the delousing stations wore louse-proof suits, which consisted of a one-piece garment covering the shoes and tied about the neck. With these precautions, which have been carried out faithfully, it is not probable that our soldiers have brought typhus infection into this country. However, now that the war is over, we may expect that immigrants will again become possible carriers of this and other infections.

The U. S. Public Health Service has provided at ports of entry for immigrants satisfactory apparatus for delousing. This differs in no essential way from the delousing stations established by the army. The stripped immigrants are sprayed with a soap solution made by dissolving one part of laundry soap in four parts of soft water and adding an equal volume of gasoline. This mixture hardens in a few hours to the consistency of a stiff jelly and constitutes the stock. For spraying, this stock is mixed with from five to ten parts of hot water. The spray is so directed as to penetrate the creases and hairy parts of the body. The face is not spared and no injury is done even if the eyes are kept open. After spraying, the individual walks through a warm spray in which he may linger until he is satisfied that the soap is washed off. For the treatment of clothing and baggage, hydrocyanic acid gas is used. The articles are placed in an air-tight room about eight by eight feet. Into this, hydrocyanic acid gas is injected from a generator situated in the open air. After sufficient exposure the gas is removed from the room by electric fans; however, this method was not found to be fully efficient, and later the articles were placed in a metal chamber in which a vacuum was produced and the gas introduced. The following are the directions: A vacuum of 25 inches of mercury is generated; then the gas from 6 ounces of sodium cyanid per 100 cubic feet is introduced slowly. The vacuum is reduced to 5 inches, where it is held for 1 hour and 25 minutes. This method has been found efficient in the disinfect-

tion of baled-cotton, which must be penetrated in order to destroy potato bugs and other insects. It should be noted here that hydrocyanic acid gas has but slight effect upon bacteria and should not be relied upon as a germicide. The advantage of this process in the destruction of insects lies in the fact that the baggage need not be opened.

It should be plainly understood that there is no evidence that typhus is carried in any other way than by the bite of lice which have previously fed on a person sick with this disease. If the transfer of lice be prevented there is not the slightest danger of contracting the disease by coming into close proximity, or even into contact, with those suffering from it. It follows that every one sick with this disease should be protected from visitation by lice. Since these pests cling to the clothing when one undresses, this precaution is easily carried out in any well-equipped hospital. There is, therefore, no reason that cases of typhus, under proper precautions, especially on admission, should not be cared for in general hospitals. Likewise, under proper precautions, one with this disease might be treated without danger to the community in his own home; however, since there are no disinfecting plants in homes the proper place for a typhus patient is in a hospital, and there his clothing should be removed and his body treated as indicated before he is admitted to the ward or room.

Virus.—The louse serves as the carrier of the virus and only infected lice can transmit disease. The nature of the virus has not been determined. One attack of typhus gives immunity. This has been shown by observation on man during epidemics and has been demonstrated by experiments on monkeys. A monkey in which typhus had been produced by the bite of infected lice or by the injection of blood from a human case and has recovered, remains immune when again subjected to the bites of infected lice or treated with infected blood. There is no known vaccine for typhus fever.

Bibliography

- ACLAND, H. W.: *Fever in Agricultural Districts, etc.*, Oxford, 1858.
 ANDERSON, J. F.: *Pub. Health Rep.*, 1915, No. 71.
 ANDERSON, J. M.: *Jour. Path. & Bacteriol.*, 1921, xxiv, 478.
 CACCINI, A. M.: *Mil. Surgeon*, 1922, 1, 403.
 DICKINSON, C.: *An Inquiry into the Nature and Causes of Fever, etc.*, Edinburgh, 1785.
 DOTY, A. H.: *Med. Rec.*, 1921, xcix, 379.
 GOLDBERGER, J., AND ANDERSON, J. F.: Reprint from *Pub. Health Rep.*, 1912, No. 82.
 JACKSON, R.: *An Outline of the History and Cure of Fever, etc.*, Edinburgh, 1798.
 LUCAS, C. E.: *On the Principles of Inflammation and Fever*, London, 1822.
 MACILWAIN, G.: *Lectures on Fever*, London, 1849.
 MACKENZIE, M. D.: *Jour. Roy. Army Med. Corps*, 1921, xxxvii, 50.
 MURCHISON, C.: *Typhus Fever*, London, 1864.
 NETTER, A., AND BLAIZOT, L.: *Compt. rend. Soc. de biol.*, 1918, lxxxi, 268.
 PALFREY, F. W., AND WOLBACH, S. B.: *Med. Clin. of North America*, 1921, iv, 1877.
 PARK, J. R.: *The Pathology of Fever*, London, 1822.

- PIERCE, C. C.: Pub. Health Rep., 1917, xxxii, 426.
- PLOTZ, H.: New York Med. Jour., 1915, ci, 853.
- PLOTZ, H., OLITSKY, P. K., AND BAHR, G.: Jour. Infect. Dis., 1915, xvi, 1.
- PRINGLE, J.: Observations on the Nature and Cure of Hospital and Jail Fevers, London, 1750.
- ROUFELL, G. L.: A Short Treatise on Typhus Fever, Philadelphia, 1840.
- WILSON, J. C.: A Treatise on the Continued Fevers, New York, 1881.
- WOLBACH, S. B., TODD, J. L., AND PALFREY, F. W.: The Etiology and Pathology of Typhus, Cambridge, (Mass.), 1922.

CHAPTER XXXIV

THE RELAPSING FEVERS

Febris Recurrens; Spirillum Fever; African Tick Fever

Description.—In widely separated parts of the world, under widely varying climatic conditions, and among all races and conditions of men, there has been recognized for a long time a group of febrile diseases, with individual differences, but with fairly constant characteristics in symptomatology. The terms “relapsing” and “recurrent” fairly express the distinguishing characteristics of the members of this group of diseases. The group may be broken up into individual diseases which are distinguished from one another by more or less marked differences in the infecting agents and more striking differences in the insects which serve as carriers of the virus in different areas.

The incubation period in these fevers, as determined by experimental and accidental inoculation, varies from three or four to ten or twelve days, but averages about seven. During the period of incubation there is no marked or plainly recognizable and distinctive departure from health, although there may be slight torpidity in bodily function, accompanied by more or less mental depression. There is, however, as we have said, nothing distinctive enough in the way of symptoms during the period of incubation to justify a diagnosis. Furthermore, during this time the parasite is not found in the peripheral blood.

The first pyrexial stage appears suddenly, with rigors, headache, pain in the back and limbs, and the usual accompaniments of an acute infection. The temperature rises abruptly, usually standing at from 103° to 104° F., but in some cases going higher. In about seventy per cent of the cases the chills ushering in this period are accompanied by vomiting. The pulse is accelerated, compressible, without diastolic murmurs, and in about five per cent of the cases there is epistaxis. There is usually some evidence of bronchial congestion and pneumonia may appear as a dangerous sequel, though this is rather unusual. The temperature of the first pyrexial stage is usually continuous, but the step-like elevation, characteristic of typhoid fever, is absent. The bowels, as a rule, are constipated. The spleen and liver are slightly enlarged and more or less tender. There is some reduction in hemoglobin, and, as a rule, a marked polymorphonuclear leucocytosis. The increase in respiration and pulse rate follows the temperature chart, and in severe cases delirium is not unknown. During this and other febrile stages the spirochetes can be

found in the peripheral blood, but the number in evidence under the microscope varies widely and is not in proportion to the severity of the attack. The first pyrexial period continues, as a rule, from four to seven days. Then there is a critical fall. The fever not only disappears, but the temperature becomes subnormal. Within a few hours the fall in temperature may measure as much as 10° .

The first apyrexial or intermission stage is followed by speedy recuperation. The temperature, subnormal at the end of the first pyrexial stage, quickly returns to normal, the fur on the tongue disappears, the appetite again puts in its demands, while the constipation is relieved and within two or three days it is difficult to convince the patient that he should continue off duty and in bed. During the afebrile stages the spirochete cannot be found in the peripheral blood, but in some unrecognizable form it must be present in this fluid at this time, because the blood still remains infectious, as can be demonstrated by inoculation of men or animals.

The intermission or apyrexial stage continues from seven to twelve days and by this time, as a rule, the patient is feeling quite well, but the second pyrexial stage appears suddenly and in much the same form and with the same accompaniments as in the first stage. The fever of this period is not likely to run so high as in the first and more frequently it is of a remittent rather than of a continuous type. The spirochetes are again present, though often scanty, in the peripheral blood. In the majority of instances complete recovery follows the second pyrexial attack, but in exceptional cases there may be repeated accessions and remissions of the febrile attacks extending through weeks and possibly months. Even in these the spirochetes reappear in the blood with every febrile accession and disappear during the remissions, but throughout both stages the blood remains infectious. Carter, as early as 1882, reporting on 441 cases in which the diagnosis was confirmed by the detection of the parasite in the blood, states that in 23.8 per cent of these there was only one febrile attack, but these were of the abortive type. A larger number presented two febrile stages, while only in five per cent were there three, and only in two per cent were there four. When there are two or more pyrexial stages, the temperature chart is characteristic of this disease. In about ten per cent of Carter's cases an eruption appeared during the first pyrexial attack, usually about the fourth day. This eruption consists of minute red blotches or stains which are most frequently seen on the front and sides of the chest and abdomen or on the arms, more rarely on the legs.

It is evident that in the pyrexial stage a germicidal substance is produced and this suddenly destroys most of the spirochetes, but there are some which resist this destructive agent and after a time these more

resistant ones multiply and bring on the subsequent attack. It has been demonstrated experimentally that serum secured after a first attack destroys the spirochetes present in the blood at the time of that attack but is without effect upon the spirochetes of subsequent attacks. A highly germicidal serum can be obtained by repeated inoculations and this has been shown to have both preventive and curative action. Novy and Knapp have hyperimmunized rats, which are subject to relapse, and in this way have obtained rat serum which possesses marked protective and curative properties as demonstrated on other animals. There seems to be no doubt that a potent serum might be prepared for this disease, but since it has been shown that arsphenamine and its congeners are specific in the treatment of the relapsing fevers, it is not likely that a serum will be used. It has been shown by Iversen, Sergeant and Gillot, and Mouzels and confirmed by others, that an intravenous injection of five grains of arsphenamine, as a rule, prevents a second attack. In some instances, however, a second attack is only delayed by this treatment, but in these a second injection of arsphenamine has proved to be permanently curative. The mortality in the relapsing fevers is exceedingly variable, depending apparently to some degree upon the species of the spirochete causing the infection. As a rule, however, the mortality is low compared with that of typhus and typhoid. When this disease attacks pregnant women abortion is quite certain to occur. The spirochete penetrates the placenta and infects the fetus, as has been demonstrated by the detection of the organism in the fetus after its expulsion.

Relapsing fevers have frequently been confounded with those of malarial origin. The demonstration of the spirochete in the blood in the pyrexial stage in the former and of the plasmodium in the latter furnishes unquestionable differentiation. There may be difficulty, especially in the first attack, in distinguishing between relapsing and typhoid fever. The presence of the spirochete in the blood and the absence of the typhoid bacillus in blood cultures are methods of diagnostic determination. In reading the history of these diseases it is evident that relapsing fevers have been occasionally believed to be yellow fever. At the present time similar confusion could hardly occur. Even in pre-bacteriologic periods, the absence of the typical black vomit of yellow fever and the greater mortality in this disease should have rendered differentiation quite certain. Dengue and relapsing fever have been confounded in former times, but the absence of the spirochete in the febrile stage renders this distinction easy.

History.—Some think that they find in the books on epidemics a clear description of relapsing fever by Hippocrates. Others think that the cases cited were intermittent malarial fevers. It is quite certain that

Hippocrates saw and described typhus fever, but that he distinguished between this and relapsing fever is certainly not true. Hirsch (1883) gives credit for the recognition of relapsing fever as a distinct disease to Griesinger, as the following quotation indicates:

“It is well known that Griesinger has the merit of having first correctly recognized the peculiar features of bilious typhoid (a name at that time accepted by Hirsch as synonymous with relapsing fever), and of having given a detailed account of the disease from the observations that he made in Egypt; he pointed out the difference between it and bilious remittent and yellow fever on the one hand, and on the other hand between it and relapsing fever, which had first become accurately known since 1842 through the Scottish physicians; and he showed that both these forms of disease were to be regarded as modifications of one morbid process. Lebert and others subsequently raised objections to the identification of relapsing fever and bilious typhoid, but as I think, without reason. I lay no stress on the facts that the two forms occur very often together in the same epidemic; for that is true also of relapsing fever and typhus, which are, without doubt, quite different processes. The decisive facts in my opinion are; that there are clearly marked transition forms between relapsing fever and bilious typhoid, which, from the point of view of symptoms and morbid anatomy, incline sometimes to the character of the one and sometimes to that of the other; and above all, that the same morbid poison underlies both forms, as we shall see later on.”

It is quite certain now that both Hirsch and Griesinger were in the wrong when they taught that relapsing fever is identical with any form of typhoid fever, either etiologically, symptomatically, or pathologically. Some years before Griesinger wrote, French physicians had quite accurately pointed out the distinctions between typhus and typhoid fevers and had emphasized the characteristic postmortem findings in the intestine in typhoid, a condition which is never seen in either typhus or relapsing fever. As we read the literature of epidemic fevers, we are inclined to give credit to Irish clinicians early in the eighteenth century for the earliest indication that under the name of typhus fever there existed in Ireland at that time both typhus and relapsing fever. Rutty, in his chronological history of prevailing diseases in Dublin, published in 1770, speaks of an epidemic in that city in 1739 and remarks that the disease was characterized by relapses occurring as many as three times.

In the early part of the nineteenth century several Irish physicians recognized the fact that the disease prevailing in their country at that time and generally known as typhus fever really consisted of two diseases. Speaking of the epidemic of 1826-1827, O'Brien wrote:

“At the commencement of the epidemic, two species of fever were distinguishable in the wards of this hospital, which, to use the language of Sydenham, we shall call the fever of the old and the fever of the new constitution. The first was the ordinary typhus of this country, marked by its usual protracted periods, running on to the eleventh, fourteenth, seventeenth or twenty-first days. This species of fever was far inferior in numerical amount to the other, but far more fatal. It became complicated in several instances with the fever of the new constitution, and assumed many of its symptoms; the delirium was more vivid than usual, often rising to phrenzy; black

crusts on the tongue, and black sordes of the teeth and gums, which usually characterize bad cases of typhus, seldom presented themselves here. Petechiae were less frequent, but the skin in many cases assumed a yellowish hue, not that intense or deep yellow which belongs to icteroid fever, a few cases only of which occurred, but the lighter shades characteristic of a bilious type. The temperature of the skin was but little increased, frequently even lower than the natural standard, and the general aspect of the disease partook more of a nervous than vascular character. The other species of fever, or that of the new constitution, which constituted the bulk of this epidemic, was one of short periods, terminating in three, five, seven, or nine days, but the second of those periods was the most frequent. In hospital practice it is difficult to ascertain the day of invasion with precision, the intellectual faculties, and particularly the memory, being impaired in most cases, and utterly obliterated in some. From the shortness of the present fever, however, the crisis was more easily ascertained than under ordinary circumstances. In the months of June and July, 1826, the author noted the day of crisis in forty cases with due caution, and of those nineteen terminated on the fifth day, twelve on the seventh, five on the eleventh, two on the seventeenth, and two on the twenty-first days. In this fever the chain of morbid actions was rapidly formed and rapidly terminated, and the disease developed itself with energy from the commencement. The access was sudden, and usually came on at midday. The person previously in perfect health would then be seized with sickness at stomach, headache, pain in the small of the back, and chilliness. On the approach of evening all these symptoms increased, and the febrile paroxysm was fully formed; the chilliness increased to a rigor, and the nausea to vomiting, which harassed the patient for the first three or four days of his fever in the form of an empty straining, and frequently continued through its whole course. On the evening of the fifth or seventh days the *exacerbatio critica* commenced, which, mostly with the intervention of a rigor, but very frequently without this symptom, terminated in a profuse perspiration, which continued through the night, so that on the following morning the crisis was complete, and we generally found the patient convalescent. We frequently received the glad tidings from himself in the following words: 'Sir, I got the *cool* last night.' The *cool*, however, was sufficiently visible in his countenance before he opened his lips, but unfortunately in many instances it proved only a delusive truce to his sufferings. The patient was destined perhaps to be harassed by one, two, or three relapses, which prolonged the whole duration of his illness even beyond that of the most protracted typhus. In fact, the liability to frequent relapses was one of the most striking characteristics by which this fever was distinguished from all previous epidemics, at least which happened in our time."

As we read the above, we are struck with the striking clinical description of relapsing fever and the distinction made by the author between it and typhus fever. The suggestion by O'Brien that the typhus fever of his practice was modified and to some extent mitigated by the coexistence of a milder infection brings up a question which now, after one hundred years, remains interesting but incapable of satisfactory solution. In the same article, O'Brien differentiates between the fever which he describes as of the new constitution and malarial, intermittent and remittent, and yellow fever. In the further description of his new disease, he says:

"It was, in fact, a long fever broken into short periods. If we could alter the type of our long fevers by art in this manner, how greatly should we lessen their mortality!

The liability to relapse in this fever was unquestionably in the inverse ratio of the duration of the disease; the five-day fevers were more liable to relapse than the seven-day, and so on. In long fevers of seventeen and twenty-one days relapse is a rare occurrence, unless under very unfavorable circumstances. The period of intermission the author thought was longer in the seventh than in the five-day fevers, but was extremely irregular in all, varying from twenty-four hours to a fortnight, or even upwards. The tendency to relapse was not diminished by full or abstemious diet, or indeed by any regulations of regimen, or any of the ordinary precautions."

In studying the literature of relapsing fever, we have found nothing of more interest than the chronicles of epidemics in Ireland. Some of these contain much wisdom, occasionally spiced with wit, and more frequently seasoned with pathos. From all the evidence that we can find, it seems that malaria has never been widely prevalent in this Island. The earliest authentic writer, Boate (1652), certainly describes, under the name of *Typhus hibernicus*, typhus fever. He wrote:

"The scurvy, an evil so general in all other northerly countries confining upon the sea, is until this day utterly unknown in Ireland. So is the quartan ague, the which is ordinary in England, and in several parts of it doth very much reign at all times. As for the tertian ague it was heretofore as little known in Ireland as the quartan, but some years since, I know not through what secret change it hath found access into this Island, so that at this time some are taken with it, but nothing near so ordinarily as in other countries."

Wylde, commenting upon the above statement nearly 200 years later, wrote as follows:

"May it (malaria) not have been then, as we know it has been in modern times, almost entirely of English origin, and carried into this country by the annual emigrants who have been its principal victims since the commencement of the present century? Such was the number of cases that presented in Ireland some years ago, among the laborers newly arrived from the fen and marsh counties of England, and who were the chief subjects of this disease, that the existence of ague as an endemic affection of Ireland, has been by some denied."

Quoting again from Boate, he said:

"As Ireland is subject to most diseases in common with other countries, so there are some whereunto it is peculiarly obnoxious, being at all times so rife there that they may justly be reputed for Ireland's *endemi morbi*, or reigning diseases as indeed they are generally reputed for such. Of this number is a certain sort of malignant fevers, vulgarly in Ireland called Irish agues, because at all times there was common in Ireland, as well among the inhabitants and the natives, as among those who are newly come thither from other countries."

All subsequent writers agree that the "Irish agues" of Boate constituted typhus fever, including therewith typhoid and relapsing fevers.

That the Irish agues included not only typhus, but relapsing fever, is quite positively shown by many of the early writers. Ruttty wrote as follows:

"Now the summary result of the observations in the following work in respect to

this matter, is, that amidst all the obscurities and uncertainties attending the seventh, fourteenth, twentieth, and twenty-first days, were nearly either the days of the most perfect crisis, or the days on which the greatest number of fevers terminated either in the recovery or death of the patient. It is true, many of our fevers did also terminate in five or six days: but the crisis in this case was commonly imperfect, the patients being subject to relapses.”

Harty, in comparing the epidemics of 1741 and 1817, wrote:

“In their characteristic symptoms, causes, and general treatment: in all which respects their coincidence was very remarkable, as also in changing, when at their greatest height, to a short fever of five or seven days’ duration, with a remarkable tendency to relapse; such change having in both epidemics immediately preceded the gradual subsidence of each.”

As further evidence of the presence of relapsing fever in epidemics of Irish ague, we offer the following quotation from Rutty:

“It seems not unworthy of notice that there was frequently a fever, altogether without the malignity of the disease already described, of six or seven days’ duration, terminating in a critical sweat, as did the other also frequently; but in this the patients were subject to relapse, even to a third or fourth time, and yet recovered.”

More than one Irish writer emphasizes the observation that the death rate was much higher among those abundantly fed than among those on scanty rations. Rutty wrote:

“The poor abandoned to the use of whey and God’s good providence, recovered, while those who had generous cordials and great plenty of sack, perished.”

Along the same line Sims said:

“The disease here described showed itself among the middle ranks of the people, whose fortune not exempting them from industry, they are exposed to many irregularities in their manner of life: who use much flesh in their diet, and whose prevailing foible is an indulgence in spirituous liquors. Among the poorer sort, whose food is chiefly vegetables, the disorder during the summer and harvest proceeded to a much greater length, but did not show such symptoms of malignity, the uncomfortableness of their houses, and want of all heating medicines, assisting to put a friendly stop to its increase.”

Irish clinicians, even those of the seventeenth and eighteenth centuries, were convinced that the disease with which they were dealing was contagious; in fact, the statement is made by more than one of these writers that Typhus hibernicus was the only contagious fever known to them. They indulged in some controversy concerning the nature of the contagion. Barker and Bancroft held that the disease never appeared in a community until the specific contagion was brought in. Bancroft held

“that specific contagions are each and severally creatures of divine wisdom and power, as distinctly and designedly exerted for their production, as it was to create the several species of animals and vegetables around us.”

On the other hand, Harty and others, while believing in a living con-

tagium, held that this might be brought into existence, especially in times of famine, by the crowding of the poor and destitute.

About the beginning of the nineteenth century special isolation hospitals for the treatment of these fevers came into existence in Ireland and the clinicians of that time believed that these hospitals were of great aid to them in reducing both the morbidity and the mortality rates. It became the custom, after a patient had been taken to the hospital, to whitewash the walls of the room from which the sick individual had been carried. Harty wrote concerning the fever hospitals, as follows:

“As regards fever hospitals, they should for the prevention of disease be maintained in an efficient condition in every large town in Ireland, and in the country villages huts appropriated for the reception of those ill of fever. The value of such establishments may be estimated by the important difference in the mortality of the epidemics of 1741 and 1817; one in every 25 persons having died with the former, and only one in every 130 by the latter. There were no fever hospitals in Ireland or elsewhere, until the commencement of the present century (1800), and their value is still further proved by the more rapid subsidence of fever in those districts, which during the late calamity were adequately supplied with these establishments.”

It became a custom when the patient was carried to the hospital, to remove all his clothing and to heat it in a stove. This probably did much to reduce the number of vermin. In insisting upon a change of clothing the physicians met with much opposition on the part of their patients, the latter asserting that the change was likely to lead them to catch cold. On this point Rogan makes the following interesting statement:

“The bed or body linen was seldom changed, even among those who had the means of doing so, lest the patient might take cold; and so great was the fear of damp, that before a shirt was thought fit to be put on the sick, it was frequently worn for a day by a person in health.”

During the centuries that these fevers prevailed so extensively in Ireland, many of the inhabitants were extremely poor and beggars in great numbers swarmed over the country. The inhabitants deemed it a disgraceful thing to turn one of these beggars from their doors without having divided with him their small store of food, and permitting him to sleep on the floor if night overtook the beggar while making his call. In the great epidemic of 1817-1819, in some sections of the country at least, huts along by the hedges were provided for these wandering mendicants and they were forbidden to approach houses. Those among them who were taken ill and were cared for in these improvised huts did quite as well as those who had homes in which they were treated, and the chronicler states:

“This plan was advantageous to the sick, as well as to the community. The former were sheltered from the rain, whilst they were exposed freely to the air, and recovered

in greater numbers than they would have done if confined in close cabins; and the convalescents were more speedily restored to strength as the neighboring inhabitants supplied them liberally with nourishment, in order to compensate for the apparent cruelty of denying them admittance to their houses.”

The epidemic of 1817-1819 led to the inspection of lodging houses, the reporting of cases of fever occurring in such places, and the placarding of houses when the patients were not removed to the hospital.

Many of the Irish physicians of that time became quite convinced that no amount of filth, so long as the specific contagion was absent, would give rise to these epidemic fevers. Chisholm cites an instance of a village in which much slaughtering of animals was done and in which the air was foul and offensive and yet the inhabitants did not suffer from the pestilence which prevailed in more sanitary places. While many of the procedures now employed in controlling epidemics had their birth in the Irish agues, so far as we can ascertain, no one up to the time of the epidemic of 1817-1819 suspected vermin as the distributors of the disease.

Rogan, to whom was set the task of controlling the progress of the epidemic of 1817-1819 on the extensive estate of the Marquis Abercorn in the north of Ireland, has left striking pictures of the economic distress under which the tenants on this estate suffered. He wrote:

“On visiting the houses where fever prevailed, I found some of them in a state of filth beyond anything I had ever witnessed. That in which the disease began had been occupied, during the winter, by a number of families, who had come from the mountains in search of employment, and had brought with them no furniture, nor any bedding except their blankets; each room was rented at a shilling per week, and the tenant, that he might be enabled to make this payment, afforded lodging to the begging poor at a penny per night. The floors and staircase were covered with filth, which had been accumulating for many months. The straw used as bedding, which had not been changed for a great length of time, was gathered into a corner of the room, in the morning, and spread over the floor at night. All who applied for lodging were received, and so numerous were the strangers from every part of the surrounding country, that 20 or more often lay in one small room. To protect themselves from the cold, every crevice, by which air could find entrance, was carefully closed. The roof was in such bad repair that the floors were always damp, and the cellars filled during the winter with stagnant water, which emitted a stench so offensive as to be perceptible at a considerable distance. * * * The clothing and persons of those received into the fever hospital proved clearly the total inattention of the poor with regard to these points. Their bodies were often so bronzed with filth that the natural color of the skin could hardly be perceived. Their hair was filled with vermin, and the smell of many was so offensive, as to render it a very disgusting office on the part of the nurse-tenders, to free them from the accumulation of dirt with which they were loaded. Their clothing was often in so foul a state that it was thought more economical to destroy it, and supply its place with new, than to attempt cleansing it, as it would in many instances not have been worth the expense of washing. This statement is applicable in the fullest extent to the begging poor, who formed a large proportion of the patients in hospital; but, with somewhat less strength of coloring,

it will serve for most of those received into that institution, except in the instances of servants brought there from the houses of persons of respectability.”

Harty, in describing the epidemic in Dublin, wrote:

“From an inspection made during the prevalence of the epidemic of the state of 160 apartments inhabited by the poor, it appeared that there were only 105 beds, occupied by 209 men, 319 women, and 285 children! Such is the state of the poor of Dublin. Surely something should be attempted to alleviate this wretchedness.”

Barker and Cheyne wrote:

“The failure of the crops in 1816 was not much felt till the spring of the following year; but scarcity then becoming general, attained its greatest height about midsummer, and extending to all the productions of the earth, occasioned extreme distress. In some places the poorer classes were compelled to the sad necessity of collecting various esculent wild vegetables, nettles, wild mustard, navew, and others of the same kind to support life; and in places distant from Dublin, wretched beings were often seen exploring the fields with the hope of obtaining a supply of this miserable food. In districts contiguous to the sea, various marine plants were had recourse to for the purpose of allaying the cravings of hunger; and we have been informed that on the sea coast near to Ballyshannon, many of the poor, during several months at this period, subsisted, either chiefly or altogether, on cockles, mussels, limpets, or even the putrefying fish they could procure on the shore. In some districts seed potatoes were taken up from the ground, and the hopes of the future year thus destroyed, for the relief of the present necessity; and the blood drawn from the cattle on the fields, and mixed with oatmeal, when this could be procured, has not infrequently supplied a meal to a starving family. So general was the distress, and insufficient the supply in some distant parts of the country, that a few unhappy sufferers are said to have died of absolute want of food, and many must have sunk under the combined impressions of hunger, damp, cold, and the anguish of mind necessarily attendant on sad anticipation of the future. * * * When fever commenced in a poor family, or was introduced by a stranger or lodger, it generally extended to all its members. The poor were the chief sufferers, in consequence of their neglect of cleanliness, particularly with respect to their clothing, and the smallness and crowded state of their apartments, evils at this time much increased by the extreme poverty which weighed them down. On the other hand, the superior classes, whose circumstances were different, their clothing more frequently changed, their persons more cleanly, their apartments less crowded and better ventilated, and among whom seclusion from the sick was practiced, in proportion to their enjoyment of these advantages generally escaped the disease. And that such exemption did not depend on any other causes than those here assigned, is proved by the great suffering of persons of this class when sufficiently exposed to contagion by communication with the sick. Thus the medical attendants on fever hospitals and dispensaries, and the clergy, more especially those of the Roman Catholic church, whose duties brought them into contact with fever patients, were very general sufferers, and considerable numbers of them became victims.”

During the fourth decade of the nineteenth century relapsing fever was widely distributed throughout Scotland, where it was known to physicians as typhus mitior and to the laity as yellow fever. According to Goodsir, the records show that during the year 1842-1843, 672 cases of yellow fever were admitted to the infirmary at Dundee, with only seven deaths. Of course, it will be understood that the term “yellow

fever'' as here used means relapsing fever and not true yellow fever. Goodsir, in discussing this fever, says:

''The fever in question did not, as far as my own observations went, and from what I can learn from others, assume a remittent form, but was continued until the period of its cessation, which was in almost every case sudden, and often with profuse perspiration. We had also almost uniformly the relapses noticed in other places, taking place about the fourteenth or fifteenth day, and generally three or four days after the cessation of the fever. These relapses did not in general remain beyond three or four days, when the patient again became convalescent. In several instances I have seen a second and sometimes even a third relapse before the patient thoroughly recovered.''

According to Orr, there were at least 40,000 individuals in Glasgow and vicinity infected in the fever epidemic of 1843-1844. At the time there were recognized the following fevers: (1) Typhus; (2) continued fever with relapse; (3) common continued fever. There is no doubt that these fevers were often mixed in making a diagnosis, and it is more than probable that under common continued fever there were many cases of typhoid. It may be interesting, however, to know that in the Royal Infirmary of Glasgow the death rates for the above fevers were as follows: Typhus, 11.7; continued fever with relapse, 3.7; common continued fever, 7.3.

Writing in 1866 of the epidemic fevers in Scotland, Stark said:

''The relapsing fever of 1841-1842, which constituted from a third to a half of the cases in that epidemic, was by many considered to be a new type of fever which had not been described by the older physicians. This was simply a mistake. It was no new form of fever, but one of the very oldest forms of fever which ravaged this country and Ireland during the last century, and likely for centuries before that. The dreadful famine fever which ravaged Scotland and Ireland a century and a quarter ago, viz., from 1740-1742, was as essentially a relapsing fever as the notorious recent famine fever of Ireland of 1846-1849, for it is recorded of the cases that 'the patients were subject to relapses even to the third and fourth time.' The fevers of the last century were described too imperfectly to enable us to trace how often this form of relapsing fever appeared among the epidemics; but the relapsing fever was recognized as constituting no small proportion of the cases in the epidemics of 1798-1800, in that of 1810-1811, in that of 1817-1820, in that of 1826-1829, in that of 1841-1842, in that of 1846-1849, and has even appeared in the epidemics at present prevailing over Scotland. Nay, more, according to the accounts which have reached us from Russia, it constitutes a large proportion of the cases of that virulent epidemic which is at present devastating that country. Here, then, we have the same type or form of fever reproduced again and again, and remaining absolutely unchanged, during at least a century and a quarter, disappearing for a few years, then all at once again constituting no small proportion of the cases in the epidemic, of which it forms a most characteristic part. This relapsing fever, however, did not cause the other forms of fever with which it was associated, to change their types, neither did it absorb all the types of fever in these several epidemics. Maculated typhus, as it was then called, maintained its character, and its mortality, as absolutely unchanged in the epidemic of 1740-1742 as it did in the epidemic of 1863-1865, and as far as can be traced seemed

to constitute about the same proportion to the relapsing fever as in our famine fever of 1846-1849."

We have made this extensive quotation because it is interesting not only in what it says about relapsing fever in Scotland and Ireland, but on account of the clear statement of a fact which we have taken occasion repeatedly to emphasize, and that is the unchanging nature and manifestations of epidemic diseases throughout all recorded history. Relapsing fever as seen today among the starving mujiks along the Volga is the same as it was 200 years ago among the peasants of Ireland.

How long relapsing fever has prevailed in Russia, in the Balkan States, Austria, and Germany, no one knows. The probabilities, however, are that the insects which are the distributors of these diseases have been occupants of these regions quite as long as have the human hosts upon which they feed. In all probability, as long as man has been a vermin-bearing animal the race has not been free from relapsing fever and fluctuations in its prevalence have been determined, largely at least, by living conditions. Like other epidemic diseases, relapsing fever has from time to time and at irregular intervals extended and contracted alternately its geographical boundaries, taking every advantage of opportunities in the way of new feeding grounds offered by alterations in the habits of man. From 1868 to 1872 relapsing fever came very near being a pandemic and it was during this period that Obermeier, of Berlin, discovered its specific virus in the form of a spirochete. Obermeier's first observations were made in 1868, but he awaited opportunity for confirmation and did not publish until 1873. He saw in drops of blood taken from patients with this disease numerous rapidly moving spirochetal bodies. This discovery was soon abundantly confirmed and since that time the detection of these bodies in the peripheral blood during a pyrexial attack has been regarded as essential to positive diagnosis.

The first to recognize relapsing fever in this country was Clymer, whose clinical acumen is shown in the following quotation:

"In June, 1844, a ship arrived at Philadelphia from Liverpool with Irish emigrants, amongst whom there had been some sickness during the voyage. Fifteen were sent to the Philadelphia Hospital, and admitted into the medical wards under my charge. They were suffering from continued fever of a kind different from any that I had then seen. I thought that I recognized, by the published histories, the kind then prevailing epidemically in Scotland and England, and which had appeared in those countries in 1843. The correctness of my conjecture was soon established. In all these cases the access was sudden, with severe headache, vomiting, muscular soreness and joint pains, rapid pulse, hot skin, a moist tongue with a creamy grey or yellowish coating, and red tip and edges (though in a few cases the tongue and mucous membrane of the mouth were quite dry for several days), enlarged spleen, no constant intestinal troubles, and no eruption. In all there was much debility from the outset, and the

face had a peculiar bronzed tint, like that of persons suffering with malarial poisoning. About the seventh day defervescence happened, with abundant sweats; the appetite became good, the expression was natural, and the patient apparently entered upon convalescence, though still complaining of muscular weakness, and the face was of a dusky yellowish hue. Near to the fourteenth day a second paroxysm suddenly occurred, in some cases with all the acuteness of the first, and lasting for five or six days, whilst in others it was slight, and passed off in thirty-six or forty-eight hours. So far as I know, there were no instances of a second relapse. I saw no sequelae, for the reason, perhaps, that patients left the hospital very soon after the establishment of the second convalescence. None of the house physicians, or nurses, or other patients contracted the fever, and the only evidence I had of its possible contagiousness was the fact, that two sisters, for some years resident in Philadelphia, being admitted with the fever, and whose brother had gone from the ship to their house, and there been taken ill. Other steerage passengers were at the time in the hospital, complaining of chills, sweating, aches, headache, debility, etc.; but none of these were ever fairly down with the fever."

From 1844 to 1869 there are short references by American clinicians to a disease seen in Philadelphia, New York, and Buffalo, which undoubtedly was relapsing fever, and which was observed only in immigrants. In the last-mentioned year relapsing fever became quite prevalent in New York and Philadelphia and was seen not only among immigrants, but among the native inhabitants. The most instructive report of that time is that of Parry, who wrote a valuable paper on the epidemic as it appeared in Philadelphia. Parry's clinical description leaves no doubt as to the correctness of his diagnosis. This observer agreed with Muirhead and Bennett, of Scotland, who opposed the teaching of Murchison, Begbie, and Flint that starvation is an essential condition in the development of this disease. Murchison had gone so far as to intimate his belief that the disease originated in destitution and overcrowding, as the following quotation indicates:

"The poison of typhus is generated by overcrowding, and destitution favors its extensive propagation; that of relapsing fever is more intimately connected with, if it is not generated by destitution, and is propagated by overcrowding."

Parry showed that there was no starvation or even scarcity of food among the patients seen by him in Philadelphia in 1869. He gave most convincing proof that relapsing fever is due to infection. He wrote as follows:

"That relapsing fever is contagious can hardly be doubted. It has already been stated that in several cases the nurses and patients occupied the same bed at night. This was allowed because the disease was at that time thought to be remittent fever. In no instance of this kind did the nurse escape, while other members of the same family did not so surely suffer. If the apartment occupied by persons sick with it be of good size and well ventilated, it appeared that they might be visited with impunity. Patients may be admitted to a healthy family among the better classes, or into the wards of a well-ventilated hospital, without propagating the disease. * * * On the other hand, small breathing space and imperfect ventilation are followed by rapid

spread of the fever, so that the whole family may have to be transported to a hospital in order to be nursed."

The first case in which the spirochete was found in the blood reported in this country is that of Carlisle (1905). The patient was a steward on a steamer plying between New York, Galveston, and Key West. Carlisle turned over the study of the spirochete in this case to Norris, Pappenheimer, and Flournoy. These men interested Novy and Knapp and from these studies a most important contribution to our knowledge of the spirochetes of the relapsing fevers resulted. Up to that time it had been held by some that the spirochete of relapsing fever is a protozoan and not a bacterium. This belief had the weighty support of Schaudinn, the discoverer of the spirochete of syphilis. Novy and Knapp demonstrated that the spirochetes of this disease are bacteria and not protozoa; that the organisms present in "onset" blood may be kept alive *in vitro* for forty days, while those in "decline" blood rapidly die out on account of the presence of a germicidal substance; that in addition to man and monkeys, white mice and rats may be infected and there is no relapse in rats; that in "decline" and in "recovered" blood there is a powerful specific germicidal body which does not originate after the blood is drawn, but exists within the living animal; that there is also present in the body an immunizing agent distinct from the germicidal substance; that Pfeiffer's phenomenon can be demonstrated, both *in vitro* and *in vivo*; that active immunity follows recovery from infection; that passive immunity can be secured by injections of hyper-immunized blood; that both active and passive immunity may last for months; that immunity may be hereditary as a result of infection in utero; that in rats, mice, and monkeys preventive inoculations can be successfully made; that the agglutination, germicidal, and immunizing properties of "recovered" blood can be used in the serodiagnosis of relapsing fever; that the tick fever of Africa is distinct from the relapsing fever of Europe; that the spirillum of the relapsing fever of Bombay is apparently different from those of the relapsing fevers of Europe and Africa; that the evidence points to the existence of a group of relapsing fevers, and that the transmission of spirilla diseases by insects and the congenital infection of mammals and eggs of insects are properties which up to the present time have been regarded as characteristic of protozoa but are now shown to be shared by this group of bacteria. They were the first to show that spirochetes are filtrable. Besides demonstrating the above-mentioned fundamental facts concerning the spirochetes of relapsing fevers, Novy and Knapp wrote in 1906:

"Yellow fever presents a marked analogy to the spirilla infections and it is not improbable that the cause of this disease will be found to belong to this group of organisms."

As we now know, this prophecy has been justified by the work of Noguchi.

Recently (1915-1918) interesting reports have come from Meader and Waring concerning endemic relapsing fever in Colorado. Meader reported five indigenous cases, in two of which the spirochete was demonstrated in the blood, while Waring reported one case with like demonstration. These reports raised the question as to the nature of the insect in Colorado which may transmit this disease. Meader found that a band of gypsies had stopped at the tent where his patients resided in Bear Creek Canyon, and he thinks that these vagrants may have left in that locality infected body-lice. Waring's single case came from the same locality in which Meader found his, and the former raises the question as to the possibility of infected lice continuing in this locality for two or three years.

Further details in the history of the relapsing fevers will follow in the discussions of the several varieties. The time will probably come when these will be grouped, either by the spirochete which constitutes the virus, or by the insect which serves in its transmission, but at present it seems best to follow other authors and classify the relapsing fevers according to their geographical distribution.

African Relapsing Fever.—The specific spirochete found in this form of relapsing fever has been named *S. duttoni* by Novy in honor of Dutton who, while engaged in the study of this disease in Africa, became infected and died. Cook, in Uganda, in 1902, probably saw the spirochetes but mistook them for flagellating malarial parasites. The spirochete of East African fever was designated by Novy as *S. kochi*. *S. duttoni* infects man, monkeys, and small rodents. It has been found, experimentally, that the period of incubation runs from seven to ten days. The duration of the first pyrexial attack averages three days. The apyrexial stages vary from one to eight days. The course of the infection is severe, and in man there may be as many as four or five relapses. The distributor is a tick, *Ornithodoros moubata*, which is widely distributed over middle and southern Africa. It seems that Nabarro was the first in Uganda to recognize in 1903 a spirochete in human blood, but on account of the delay in his publication, priority is given to Ross and Milne and to Dutton and Todd, who reported their observations in 1904 and 1905 respectively. Dutton and Todd incriminated the tick immediately, as is shown by the title of their report, "The Nature of Human Tick Fever in the Eastern Part of the Congo Free State." In 1918 Manson and Thornton, after making examinations of members of almost every tribe in East and West Africa, reported on 1,500 cases. They found *Ornithodoros moubata* in areas in which relapsing fever occurs; on the other hand,

"camps and areas which did not contain *O. moubata* never yielded any cases of relapsing fever, the single exception being a case of a white British rank, who contracted the disease after only three weeks residence in East Africa, all of which time he spent

at a camp near the sea. Here thorough search failed to reveal ticks, and the manner of his infection must remain a mystery.”

They make the following statements concerning *O. moubata*:

“These ticks are extremely resistant to heat and to germicides, and appear to be able to exist for very long periods deprived of food and air. We have had some specimens without food in test tubes sealed with paraffin wax for over nine months, which are still alive, and a case has been quoted to us of ticks remaining alive in a bottle for four years without food. Their habitat is essentially the loose sand of the floors of the native houses; when the floors are beaten hard, they are usually found in the earth around the poles supporting the house, as owing to the action of the wind on these poles the earth immediately around them becomes slightly loose; we have seldom found them at a depth greater than six inches, either in the soil or around the poles. Statements to the effect that ticks were to be found in banda roofs in Dar-es-Salaam proved to be without foundation as far as we could ascertain. Prolonged search of many roofs in the Military Labor Corps area produced nothing but a varied collection of fleas, lice, etc. Ticks manifest great antipathy to light, remaining in the sand throughout the day, and only appearing to feed on the inmates of the house at night; the presence of a lamp even appears to afford a considerable amount of protection.

“Eggs are deposited in the sand; from observations on ticks kept in test tubes, it would appear that each tick lays some one hundred to three hundred eggs, in batches at short intervals; these eggs hatch out into ticks after an interval of about sixteen days; the nymphs are complete replicas of the full-grown insect, except that they are of a light brown color and have relatively longer legs; they possess four pairs of legs from the moment of hatching out. As regards the ticks collected from various areas, between six and seven hundred were examined microscopically and of these twenty-nine per cent were found to be infected with *S. duttoni*. Taken generally those collected from different camps all showed much the same percentage of infection, with the exception of those obtained from the West African Carrier Depot, Dar-es-Salaam, a camp which yields a particularly small number of ticks proportionate to the number of cases of tick fever occurring; these ticks were, however, very heavily infected, no less than fifty-five per cent harboring the spirillum. It is highly probable that our estimates of the percentage of infection are considerably on the low side, as, owing to the numbers to be dealt with and the dearth of skilled assistance, only a comparatively cursory examination could be given to each slide (the Germans are reputed to have found over fifty per cent of ticks infected along the main caravan routes of German East Africa). A number of eggs were also examined microscopically for spirilla, all with negative results.”

Koch found spirilla in the eggs of the *Ornithodoros* in East Africa.

According to Dutton and Todd, *O. moubata* is greenish-brown in color, and the female is about 8 mm. in length and 6 mm. in breadth. In its habits it resembles the common bedbug, living largely in native huts, hiding during the day in cracks in the wall and in the thatched roofs. It feeds slowly and may remain attached to its host for two or three hours. When replete with food its body may be distended to the size of a cherry. It attacks both man and beast, and a meal of blood seems to be favorably connected with the deposition and hatching of the eggs. These ticks may be carried long distances, especially in blankets and tent equipage. It

seems quite certain that the tick does not inject the spirochete into the body while it is biting. While engaged in feeding it deposits its fecal material on the skin and inoculation results from scratching. There is, however, some difference of opinion concerning this matter.

In case of the louse, Nicolle and his coworkers have supplied convincing evidence that the virus is not transmitted in biting.

It is still a question whether African relapsing fever is distributed by any other insect than *O. moubata*. Nearly all African huts are occupied by great numbers of insects, which vary in kind and number in different localities. Chiggers, bedbugs, fleas, and lice, sometimes one, sometimes two or more, of these, are found everywhere, but their distribution seems to bear no direct relation to that of relapsing fever. Furthermore, although frequent microscopic examinations of the contents of these vermin have been made, the spirochete has never been found in them. There is another tick, *O. savignyi*, the geographical distribution of which overlaps in some places that of *O. moubata*, and it may be proved that this insect serves as an auxiliary to its near relation in the distribution of the spirochetes. *O. savignyi* has eyes and is diurnal in its habits, while *O. moubata* is blind and commits its depredations only by night.

European Relapsing Fever.—The spirochete causing this disease is that discovered by Obermeier and is known as *S. obermeieri* or *S. recurrentis*. It is infective to man and monkeys and to small rodents only after passage through monkeys. In man the incubation period is about seven days; the first pyrexial attack continues for about the same time or a little less. The first apyrexial intermission lasts from seven to ten days and there are two, possibly three or more, relapses. Its distributors are lice, *P. humanus*, possibly *P. capitis*, and the bedbug, *Cimex lectularius*. When a louse which has bitten an infected person is examined from time to time, it is found that the spirochete disappears from the alimentary canal after about four days but reappears in the excretory passages about the ninth day. Even when the spirochete cannot be detected microscopically in any part of the louse the presence of this organism in the insect can be demonstrated by inoculation. It is not believed that the infected louse infects an individual directly while feeding, but that infection results from the crushing of the insect in scratching. It may be said, however, that Rocha Lima has transferred relapsing fever to a volunteer under conditions which rendered infection through the feces impossible. This disease has been known in every part of Europe from Archangel in the north to Constantinople and Rome in the south. It is at present (1922) endemic in southern Russia and is occasionally brought to America by immigrants, especially those from southern and southeastern Europe. Since insects serving as distributors in this disease are carried on the body and in the clothing, this form of relapsing fever may appear in any

part of the world visited by one bearing the infection. It has been seen so frequently in northern Africa that it is sometimes designated as North African fever.

Persian Relapsing Fever.—This form of relapsing fever seems to be indigenous to northern Africa, Palestine, and Persia. The spirochete is known as *S. berberum*. It is infective to man and monkey. The period of incubation in man is widely variable. The first pyrexial attack lasts from two to eight days and after irregular intervals is likely to be followed by two or three relapses. Its distributor is a tick, *Argas persicus*. This insect is widely distributed, being found on every continent. Its habits are practically those of the bedbug. It lives in the house, hides in cracks in the walls and floors, behind pictures, and elsewhere during the daytime and seeks a feeding place at night.

This form of relapsing fever is sometimes known as Mianèh fever, from a small village in Persia which has long had an evil reputation on account of the prevalence of this disease. In old Persian literature there are some interesting stories concerning Mianèh and its dangerous bug. It is said that this village has had this undesirable inhabitant from time immemorial. During the winter it lies dormant, but springs into full life and activity as warm weather comes on. It is claimed that the bug has established a truce with the native inhabitants and no longer feeds upon them, but that it wages a cruel war against the stranger and a visitor who spends the night within the gates of this city may receive a mortal wound. Stories are told of visitors who have contracted the disease and have died in great agony within 24 hours. However, Harold visited this region with English soldiers in 1919 and some of his party became infected with this disease. He gives the following description of the spirochete:

“The spirochete may be said to be longer, a little coarser than the Indian variety and its spirals are more regular and deeper, the Indian spirochete being less regular and possessing open flexures. Its length without showing divisional characters averages from 18 to 22 microns and short forms are rarely seen. On one slide a spirochete 35 microns in length was seen by me without any attempt at division being visible in the protoplasm. Figures of eight and loop forms are met with.”

Harold writes as follows concerning this type:

“In this Persian type of relapsing fever the first attack of fever may last anything from one to five days, usually three days, and the temperature of the patient is rarely as steady as in the Indian variety, the chart showing a very swinging type of fever with remissions which may touch the normal line. Profuse sweating accompanies the fall of temperature. The first apyrexial period may be anything from one to five days and is usually two days. The subsequent relapses rarely exceed forty-eight hours in duration and may last twelve hours only. They take place at fairly frequent but irregular intervals, the period of apyrexia getting longer as the disease progresses. The largest number of relapses noted by us was seven and these occurred within a period of forty-two days. In all probability many more would have been recorded if the disease in all cases had not been cut short by the administration of neosalvarsan. During

the course of the disease the patient becomes progressively weaker, anemic, debilitated and wasted. Splenic and hepatic enlargement is usual. Between the relapses the patient feels well and is cheerful. Bronchitis and epistaxis were observed in two of the cases and jaundice in one case only. The swinging irregular type of fever with short and irregular apyrexial periods and numerous relapses is diagnostic of the Persian variety and in this it is comparable to African relapsing fever, which is also tick borne."

A louse-borne relapsing fever has been reported by Sinton from Meshed in northeastern Persia. Spirochetes were detected in the lice and delousing stopped the epidemic. There were no fatalities among 31 cases. Relapsing fever has been long known in northern China and this disease played an important rôle in the late (1921) famine. It also occurs in southern China, Tonkin, and Madagascar.

Indian Relapsing Fever.—The spirochete responsible for this disease is *S. carteri*. It is easily transmissible to monkeys and from monkey to monkey, and in this passage its virulence seems to be increased. The disease is more severe than the European variety and a considerable percentage of the deaths occur in the first attack. As a result of this, clinical diagnosis is rendered difficult and uncertain and search for the spirochete in the blood is desirable. The incubation period is placed at about seven days. The first pyrexial attack lasts from five to seven days, and the apyrexial intermissions run from five to fourteen days. Transmission is affected through the louse, *P. humanus*, and through the bedbug, *Cimex hemipterus*.

That relapsing fever is indigenous to India is believed to be true by Chevers and others who have gone minutely into this subject. Jamieson has left a description of an epidemic in India in 1816 in which he states that relapses were common and that the disease was not malaria, as was demonstrated by the fact that preparations of Peruvian bark had no effect upon it. Lyall described an Indian epidemic in 1852, and this description has been epitomized by Chevers as follows:

"It was epidemic, it was distinctly contagious, it was extremely prevalent, out of 226 houses in one village, 131 were found to have been visited by the disease; and of the 949 inmates of these houses, 411 (or nearly one-half) were attacked by it. This fever presented a characteristic in which the relapsing fever of India has generally been found to differ from that of Europe—it was very destructive to life,—out of 410 attacked, 125 had died, and 126 remained sick when the report was made. * * * The most remarkable feature in this complaint is its tendency to relapse from two to ten days after the subsidence of the previous attack, without any irregularity on the part of the patient, in the way of exposure or diet, to account for it. These relapses are always attended with great derangement of the bowels, and often seem to depend upon a low degree of gastroenteritis. A large number of people are carried off from the chronic dysentery arising from this cause. The convalescence in all is remarkably slow, and many months are always necessary before their health becomes anything like reestablished."

In 1877 there was a severe epidemic in western India and Carter, then stationed at Bombay, demonstrated the presence of the spirochete in the blood, and, finally, in 1882, published his book on spirillum fever, which has become a classic. Carter gives the following description of conditions existing at that time in western India:

“This year (1877) witnessed the severest sufferings, and descriptions have been published by eye witnesses of the prevalent distress, in terms which would be difficult to surpass. Cattle died of starvation and the fields went untillied; there was no food but what was imported, and every sort of edible plant was consumed; even water to drink was often scarce. The aspect of the parched land in the eastern areas was compared to that of a desert, with a sky of gloom. Houses or whole villages were abandoned, and cherished personal ornaments were given up for coinage in large quantities by the better class of ryots. Migrations further extended, but many of the infirm, poorer, and low caste would not leave their houses, though confronted with the prospect of death from privation. Whilst facilities for the importation of grain, with means of direct public aid, were liberally afforded by the authorities, and private charity abounded, yet it would seem impossible to concur in the view that at this time only a few persons died of actual want; and how many thousands of all ages sank under the consequences of prolonged starvation, has never been adequately estimated.”

Carter showed that the spirochete is always present in the blood during the pyrexial stage but disappears during the intermission. This led him to make the following remarks:

“There is always present and commonly manifested a tendency of the disease (as estimated by fever) to recur at definite periods; the successive recurrences becoming briefer and separated by longer intervals. Recollecting the circumstance (which may be termed a biological fact), that each apyretic interval is strictly the incubation period of the following febrile event—the two forming a complete cycle, it will be found that these inclusive phenomena of a complete relapsing attack present a certain order, which cannot be regarded as accidental. Though abnormally placed in the blood, the spirillum as a living plant must be supposed to retain something of that periodical order of growth which belongs to the vegetable kingdom; and since it first appears, and then reappears, solely in connection with the febrile stages of disease, the inference becomes inevitable, that the periodic recurrence of fever is intimately associated with corresponding growth stages of the parasitic organism. From this point of view, the tolerably regular succession of relapses becomes comprehensible; and since in the blood is not the natural habitat of the spirillum (as is shown by its more or less rapid decay), it would be sufficient to establish its association with the morbid phenomena, if a moderately exact conformity in time be made apparent.”

It may be injected here that Carter believed the spirochete to be a bacterium and it was so regarded until the false teaching of Schaudinn led to the belief that it is a protozoan. The researches of Novy led to a return to a belief in the bacterial nature of this organism, as was held by Carter quite forty years ago.

Carter inoculated monkeys with fresh blood, with dried blood, and with the saliva of patients. The first, or the fresh blood, proved to be infectious to monkeys, while inoculations with dried blood and with saliva

were negative. It is interesting to note that the animals inoculated with the saliva of patients died of a septicemia, undoubtedly due, as was afterwards demonstrated by Sternberg, to the almost universal presence of the pneumococcus in the secretions of the mouth.

Carter called attention to the fact that this disease may be acquired at autopsy. He himself had two attacks at an interval of about two years, and it may be well for us to state here that the agency in the transmission of this disease is not necessarily an insect. There have been several cases of laboratory infection with the spirochetes and the greatest care is necessary in handling these organisms in the laboratory and in avoiding infection at autopsy. It should be plainly understood that, although Carter recognized the fact that the prevalent famine increased the death rate, no amount of destitution could originate the disease and that famine is not an essential condition in causing epidemics. Like other infectious diseases, relapsing fever is favored in its development and spread by any condition which brings large numbers of individuals into close contact, and quite naturally, when the crowding is due to destitution the more intimate will it be and the more favorable will be the conditions for the dissemination of the virus.

American Relapsing Fever.—We have already given the history of the first detection of the spirochete in the blood in the United States by Carlisle and of the researches made upon this organism by Novy and Knapp. This spirochete has been designated by Schellack as *S. novyi*. It induces in man a mild form of the disease, but is more severe in experimental animals. It is transmissible from man to monkey, from monkey to monkey, and from mouse to mouse. In man there is rarely more than one relapse. The incubation period varies from five to seven days. The first pyrexial attack lasts about the same time and the apyrexial intermission continues from seven to ten days. It is believed to be transmitted by the louse, but further data are needed on this point. In rare cases this form of the disease, even in man, is severe and there may be hemorrhages from the nose, stomach, bowels, or kidney. How widely this organism is distributed we do not know. As we have stated in giving the history, relapsing fever was recognized by Clymer in this country in 1844, but that was among emigrants from Ireland and it is not at all probable that the species causing the infection at that time is other than *S. obermeieri*.

In 1908 Darling reported relapsing fever on the Canal Zone, and in 1921 Bates, Dunn and St. John saw this disease in two groups of boys, who, at different times, had slept in a Chinaman's hut. The ticks, identified as *O. talaye*, were found in the bed and volunteers inoculated with macerations of these bugs developed relapsing fever with the spirochetes in their blood.

Prevention and Eradication.—It must be evident from what has been

said that in attempts to prevent and to eradicate relapsing fever we must give especial attention to those insects active in its distribution. It follows, therefore, that the methods of procedure will vary with the agent of transmission, whether it be a louse, a bedbug, a tick, or possibly other insects. In the chapter on typhus fever, we have gone into some detail concerning effective methods of delousing and these will not be repeated here. When the incriminated insect is a bedbug, methods for stamping out the disease must be quite different from those employed when it is a louse. The bedbug is inclined to live during the daytime in cracks in the floors and walls and at night it seeks the occupant of the bed. Where wooden bedsteads are used, these pests may be found during the daytime in the cracks and joints of the bed where they may be easily detected and destroyed. As we know from personal experience in traveling through Russia 20 years ago, in the houses of the mujiks and in all hotels frequented by these people bedbugs were present in great numbers. They overflowed all the cracks in the walls and could frequently be seen crawling across the floor, but even under these conditions one could sleep with safety in an iron bed, provided it did not touch the wall and each leg stood in a pan of kerosene. At that time in certain localities in Russia health officials took advantage of the inclination of the peasant to indulge in a steam bath, and while he was cleansing his body in this very efficient manner his clothes were deloused.

Protection of the traveler against the bite of the African tick when the former visits the domains of the latter is a difficult thing. Travelers are advised to avoid native houses, especially at night; not to camp near native houses or on sites used by natives; if compelled to sleep on the ground to wrap oneself thoroughly in mosquito netting and to inspect one's blankets carefully every night before retiring; in other words, to make oneself, especially at night, tick proof. It is said by those who have traveled in infested parts of Africa that with attention to these measures the risk of infection may be regarded as small.

When one takes up a more or less permanent residence in a tick infested district the difficulty of protecting himself against this predatory insect becomes more difficult. The tick lives in red sand and may be found in this to a depth of from four to six inches. If the house can be set upon posts and these be protected constantly by surrounding them with some insecticidal solution, ticks may be kept out of the house, but in most localities the only floor the house or tent has is the sand and it remains to make this so hard that the tick will not penetrate it. Manson and Thornton report their experiences as follows:

"The provision of a thoroughly hard floor impermeable to the tick appeared to us to be a first essential; the provision of concrete for such a very large number of floors as required treatment being impracticable in Dar-es-Salaam, it became necessary to

find some local substitute; this was supplied by *ant-heap earth*, of which a large quantity was present in the locality; it was beaten hard on the floors to a depth of at least four inches and allowed to set; afterwards a top dressing of *cow dung* was smeared over the whole surface to a depth of half an inch in a liquid condition; afterwards, the surface was treated once weekly with a watery solution of cow dung to maintain it in good order. The following experiment, several times repeated, showed the efficacy of cow dung. Three tins were taken, the first containing pure liquid cow dung, the second twenty-five per cent cow dung in ant-heap, and the third only moistened ant-heap; some thirty to forty ticks were mixed with the contents of each tin, and the tins were stood in a large tray of pure creosol and left for 24 hours. Examination of the contents at the end of this time showed that the ticks in the pure cow dung were still present alive, the slimy consistency of the dung having prevented their climbing out; those in the pure ant-heap were also present and showed no antipathy to their surroundings; but those in the twenty-five per cent dung had all without exception crawled out of the tin and immersed themselves in the creosol in an endeavor to escape; this very marked antipathy of the tick to cow dung appeared to us to be worthy of incorporation in our measures for the prevention of the disease. Accordingly, all floors in the area were laid down in the method described (ant-heap and cow-dung) and the results obtained were found to be highly satisfactory. Such floors give a hard even surface, and permit of being very cleanly brushed out every day; they also wear well, do not smell, and their provision is in our opinion one of the most important factors in the prevention of the disease.”

Provided there is no animal reservoir for the spirochete, relapsing fever will disappear with improvements in living conditions and when these have reached a stage in which man ceases to be a carrier of vermin.

Bibliography

- BATES, L. B., DUNN, L. H., AND ST. JOHN, J. H.: *Am. Jour. Trop. Med.*, 1921, iv, 183.
 CARLISLE, R. J.: *Jour. Infect. Dis.*, 1906, iii, 233.
 CARTER, V.: *Spirillum Fever*, London, 1882.
 CLYMER, M.: *Fevers; their Diagnosis, Pathology and Treatment*, Philadelphia, 1845.
 GOODSIR, H. D.: *Edinburgh Med. Jour.*, 1845, lxiii, 134.
 HAROLD, C. T. H. H.: *Jour. Roy. Army Med. Corps*, 1920, xxxiv, 484.
 HARTY, W.: *An Historic Sketch of the Causes, Progress, Extent and Mortality of the Contagious Fever Epidemic in Ireland*, London, 1820.
 MANSON, J. K., AND THORNTON, L. H. D.: *Jour. Roy. Army Med. Corps*, 1919, xxxiii, 97.
 MEADER, C. N.: *Colorado Med. Jour.*, 1915, xii, 365.
 NORRIS, C., PAPPENHEIMER, A. M., AND FLOURNOY, T.: *Jour. Infect. Dis.*, 1906, iii, 266.
 NOVY, F. G., AND KNAPP, R. E.: *Jour. Infect. Dis.*, 1906, iii, 291; *Science*, 1908, xxvii, 648.
 OBERMEIER, O.: *Centralbl. f. de med. Wissensch.*, 1873, xi, 145.
 O'BRIEN, J.: *Transactions of the Association of Fellows and Licentiates of the King and Queen's College in Ireland*, 1828, v, 514.
 ORR, R. S.: *Edinburgh Med. and Surg. Jour.*, 1845, lxiii, 387.
 PARRY, J. S.: *Am. Jour. Med. Sc.*, 1870, lx, 336.
 ROGAN, F.: *Observations on the Condition of the Middle and Lower Classes of Ireland as it Tends to Promote the Diffusion of Contagious Fever; with the History and Treatment of the Late Epidemic Disorder*, London, 1819.
 RUTTY, J.: *Chronological History of the Weather and Seasons and of the Prevailing Diseases in Dublin*, London, 1770.
 STARK, JAMES: *Transactions of the Epidemiologic Society of London*, 1867, ii.
 WARING, J.: *Am. Jour. Med. Sc.*, 1918, clv, 819.
 WYLDE, W. R.: *Edinburgh Med. and Surg. Jour.*, 1845, 249.

CHAPTER XXXV

TRENCH FEVER

Description.—Beginning in the fall of 1915 many cases of a disease characterized by febrile relapses appeared in the British Expeditionary Force. At first most of these came into hospital under the diagnosis of P.U.O. (pyrexia of unknown origin). Later the name “trench fever” came into general use. Subsequently this disease was found to exist also in French troops, in Italian soldiers, and in English soldiers as far east as Mesopotamia. Later still, it was reported as existing in the German and Austrian Armies. There has been much discussion as to whether this is a new disease, or one, which, under various names, has existed from time immemorial. Some have attempted to identify it with quintan fever, described by Hippocrates, Galen, and others. As epidemiologists, it would be of little value to us to inquire minutely into this discussion. The period of incubation has been found, both by observation and experiment, to vary greatly—from five to thirty days. This probably indicates the wide variability in the virulence of the organism. The prodroma of the incubation period are headache and pain in the limbs, sometimes accompanied by slight fever. Generally the onset is sudden and is accompanied by headache, dizziness, pain in the legs and back and behind the eyeballs, particularly when moved, nystagmus on turning the eyeballs sideways, injection of the conjunctivae, and a sharp rise of temperature, often going from 103° to 104° F. In more than one-half the cases the fever subsequently assumes a relapsing character. The spleen is found to be enlarged; erythematous spots or papules occur in from seventy to eighty per cent of the cases. These spots are most abundantly seen over the chest, back, and abdomen. As a rule, they are pink in color, not rising above the surface of the skin, disappear on pressure, and generally measure from about 2 to 4 mm., although occasionally they reach a diameter of 6 mm. In some cases this rash is distinctly papular. In rare instances, as many as 200 of these spots may be counted on the body. They are most abundant on the second or third day and frequently disappear within less than 24 hours. The fever is quite variable, usually consisting of an attack which lasts one week or less. In some instances the initial fever is much more prolonged and continues for six or seven weeks. In rare instances it persists from 40 to 60 and even more days, with only slight remissions. The leucocyte count is variable. An increase in the leucocytes is more likely to manifest itself at the time of a relapse. The urine often shows a trace of albumen, but evidence of true nephritis does not occur.

Transmission.—The first experiment incriminating the body louse as the distributor of this disease was made and reported by Davies and Weldon early in 1917. From this report we make the following quotation:

“Some scores of lice were collected and starved in captivity for three days. A number of them died. Two pairs of these survivors were taken and allowed to bite, under a watch-glass, two patients suffering from trench fever in an acute stage. After allowing them to feed for about 15 minutes their meal was interrupted, and each of us then allowed a pair to feed upon himself, strictly confining their sphere of operation by means of a securely fixed watch-glass. The one of us whose duties did not bring him into the wards subsequently, 24 hours later, allowed a pair to have a further meal on himself. Twelve days later very interesting developments took place. The characteristic symptoms manifested themselves, and he passed through a most typical attack of the condition of the average sufferer, with the pains and other features all present. It may be further noted that the victim had not at any time been nearer to the front than the base, nor had he been subject to any previous similar attack.”

Later, an English commission proved that the disease could be transmitted from man to man by injecting the blood of the infected into susceptible persons. This Commission attempted also to determine what part of the blood was infective, the fluid or cellular elements. The blood for inoculation was taken from cases in the febrile stages. Seven men were inoculated with the whole blood, from 5 to 10 c.c. being injected. All of these developed the disease. One was inoculated with clear serum and remained unaffected. Another, inoculated with serum tinged with coloring matter, developed the fever, as did also one who was inoculated with the hemoglobin-tinged plasma. Two were inoculated with red-blood corpuscles which had been washed several times with saline solution. One developed the disease, while the other did not. Six were inoculated with serum filtered through Berkefeld filters, but these were kept under observation too short a time to be sure about the results. Two were inoculated with filtered plasma and two with filtered extract of ground red corpuscles. None of these developed trench fever. The conclusion reached at that time by this Commission was that the virus is contained in the red corpuscle. In 1918 the Commission authorized by the American Red Cross began its investigation. This Commission has studied the matter thoroughly and has made a report in a volume which contains the important literature of the subject. Its experiments show that the blood taken from patients in the early stages of trench fever is always infective and will produce the disease when inoculated into healthy men. It disagrees with the English commission in holding that the virus is intracorpuseular. The conclusion concerning the filtrability of the virus in the blood was left in some uncertainty. The Commission found that both filtered plasma and filtered serum did not induce the disease. However, before filtration, cen-

trifugalization had been resorted to, and it is possible that the virus was thrown into the sediment along with the red corpuscles but is not intracorpuseular. Bruce had previously shown that when the feces of the louse is placed upon the scarified skin of man and rubbed in, the disease is transmitted, and the Red Cross Commission showed that the excrement of the normal louse, or one which has not fed upon a trench fever patient, will not produce the disease. The Red Cross Commission tried filtration of extracts from the excrement of trench fever lice. A portion of such dried feces was ground in a mortar, suspended in saline solution and the suspension filtered through a Chamberland L. filter, with 760 mm. of mercury vacuum during three hours. Aerobic and anaerobic cultures of the filtrate gave no growth. Three volunteers were inoculated with a portion of this filtrate, while four others were inoculated by scarifying the skin and rubbing in a portion of the same moistened feces unfiltered as a control of the infectivity of the excrement used in the filtration experiments. Two of the three volunteers inoculated with the filtrate developed trench fever, one after five days and the other after twenty days. The Commission concludes, therefore, that, at least at one stage of its development, the virus of trench fever is filtrable and ultramicroscopic. It is worthy of remark that this does not prove that the virus as it exists in the blood of man while suffering from the fever is filtrable.

Inasmuch as it has recently been stated by an authority on this subject that the disease is not transmitted by the bite of the louse but by the patient scratching the feces of the louse into his skin, we shall present, somewhat in detail, the findings of the Red Cross Commission on this point.

“After having shown conclusively by fourteen positive experiments in the first group that the louse transmits the disease living under natural conditions, experiments were performed to show whether this insect may transmit the disease by its bite alone when living under natural conditions or under unnatural ones in entomological boxes and biting through chiffon, and when no scarification of the skin, no scratching, and no crushing of the louse occurred. Five experiments of this nature have been performed all of which resulted positive. In two of these the lice only remained on each individual in the cell for a period of approximately four days and in one for seven days, and in all there was no scratching and no evidence of any abrasion of the skin. The incubation periods in these cases were 15, 14, and 30 days respectively. * * * In two instances the lice, which produced the disease by their bite alone, were kept confined in the small round entomological boxes in an incubator; during the time of biting the experimental subjects, which occurred twice daily, the box was removed from the incubator, the cover taken off, and the box covered with chiffon, and then bound upon the lower surface of the arm of the subject. The arm was held with the box underneath, so that the lice were compelled to bite upwards through the chiffon. The feeding lasted about half an hour, when the box containing the lice was removed from the arm and replaced in the incubator. Obviously, by biting in this manner, while

contamination of the skin by louse feces was reduced to a minimum, the lice lived and fed under artificial conditions, so that a negative result might not have been conclusive in relation to the transmission of the disease by the bite of the louse alone. However, both of the experimental subjects bitten in this manner developed the disease. The period from the time the lice were first allowed to bite the volunteers to the time of development of the disease was in one of these cases 27 days and in the other 38 days."

The Red Cross Commission showed (what was already known) that trench fever may be produced in an artificial manner by scarifying the arm and rubbing in, as in vaccinating against smallpox, a small amount of the excrement of lice which had fed upon trench fever cases, the excrement being collected from the sixth to the nineteenth day after the first feeding. In these instances it was found that the incubation period of the disease varied from seven to eleven days. As to the possibility or probability of this method of infection occurring naturally, the Commission makes the statement:

"This method of infection has not been demonstrated to occur naturally, and while it probably sometimes takes place it would appear to do so relatively rarely, for in our 18 experimental cases of trench fever transmitted by the louse living under natural conditions, in some of which the skin was scarified naturally by scratching and in others artificially, as well as in two pure biting experiments through chiffon, making 20 positive cases in all the incubation period of the disease has never been less than 14 days and has varied from 14 to 38 days. The inoculation by scarifying with louse excrement may be compared to that with scarification of urinary sediment or with intravenous injection of the blood of trench fever cases. The incubation period of the disease produced by the louse excrement corresponds more nearly with that produced by direct mechanical inoculation of the blood."

The Commission shows that the same group of lice may infect multiple subjects. For instance, one group of infected lice was permitted to feed successively upon five healthy men, with intervals between the feedings of from 48 to 60 hours, and in all trench fever developed. It might be objected that there is no proof that any one individual louse of the group infected more than one man. In like manner it was shown that infected lice may retain their infection and transmit it for as long a time as 13 days. The Commission concludes from this that the transference of the infection by the louse is certainly not accomplished simply by a mechanical transference of the virus, and it points to a multiplication of the virus or an intermediate life-cycle of the organism within the louse. The Commission also finds no evidence that the louse is infective until six or seven days after the time of first biting a trench fever case, and states that the louse does not retain the remnants of its food ordinarily for a longer period than several hours.

It follows from what has been said that a man may develop trench fever from 10 to 23 days after infected lice have last fed on him, and the man sick with this disease may at the time of the onset be entirely free from lice.

The weight of evidence seems to be that in nature the virus either multiplies within the louse or undergoes a cycle within it before infecting man. We make the following further quotation from the report of the Red Cross Commission:

"By 18 of our experiments it has been shown that the louse transmits trench fever when living under natural conditions, and this is apparently the common and usual means of transmission of this disease. That the infection may occur from the bite of the louse living under natural conditions, or from the crushed louse or the contents of its alimentary canal being rubbed into the scratched or otherwise abraded skin, also appears evident. Whether the louse in biting usually transmits the disease by introducing into the blood of the human host the virus contained in material from its salivary glands or in its coelomic fluid or any material from its alimentary canal is of no practical importance, although it is of some scientific interest. In order to determine definitely just how the infection is introduced by the bite of the louse it would be necessary to perform many experiments in which the insect would have to be compelled to live under artificial conditions, which might destroy the virus or prevent its developing, yet, even if positive results were obtained, no information of any practical value would be ascertained. Accordingly, we did not feel justified in exposing more healthy volunteers from our army to such experiments and infecting more of them with a disease of this nature, and in doing this consume much valuable time to prove a point of so little practical importance. Such experiments should certainly constitute no part of a war research of this nature. In typhus it is said that the louse may transmit the disease by its bite, and that it may also be transmitted by the inoculation of the skin with a crushed louse or with its excrement, but we also know less of the exact method of introduction by the louse of the virus in typhus fever than we do in trench fever."

The virus of trench fever is not found in the feces of men suffering from this disease, but it is present in the urine and may be present in the sputum of such patients. The possibility of infecting others through the urine or the sputum of the sick is quite remote. Swallowing such sputum or even such urine would have no effect. The only way in which infection could result from either of these sources would be by scratching the material into the skin; and such happenings would be rare indeed. However, in treating cases of trench fever in a hospital, in addition to delousing, it might be well to disinfect the urine and the sputum. Of the latter there is seldom any in this disease.

Eradication.—It will be seen from what has been said that the weight of evidence at present is that trench fever is distributed by the louse and that in nature it is not transmitted in any other way. The eradication of this disease is therefore, as it is in regard to typhus, a question of delousing, the details of which have been given in the discussion of typhus fever.

Bibliography

Trench Fever Report of Commission of Medical Research Committee of American Red Cross, Oxford University Press, 1918.

CHAPTER XXXVI

EPIDEMIC JAUNDICE

Weil's Disease; Icterus Gravis; Spirochetosis Icterohemorrhagica

Description.—This is a specific infectious disease, usually, but not invariably, accompanied by enlargement of the liver and by jaundice. The infecting agent is a spirochete known as *Leptospira ictero-hemorrhagiae*, the reservoir of which is the rat. After an incubation period which, in experimental animals has proved to be from five to seven days, there is a sudden onset, with chill, headache, vomiting, and diarrhea. The fever is irregular, moving quickly up or down within short periods, but generally confined to the limits of 103° to 105° F. In most cases jaundice appears on the second or third day, first showing itself in the conjunctivae and then developing rapidly over the entire body surface. The color is some shade of yellow with occasionally a greenish tint. Itching is a frequent accompaniment. In severe instances there may be minute hemorrhages in the conjunctiva, skin, or on mucous surfaces. The feces are not highly colored. The pulse is slow and the blood pressure low. In moderate cases the fever terminates by lysis from the twelfth to the fourteenth day. In most instances the liver is enlarged, and at autopsy the gall bladder is found at least half full. There is no stoppage of the gall ducts. There may be a moderate fatty degeneration in the liver. It is reported that the urine after the fifth day frequently develops a marked greenish tint on the addition of a few drops of acetic acid.

History.—In the English edition of his Handbook of Geographical and Historical Pathology, published in 1886, Hirsch has assembled thirty-four epidemics, beginning with that described by Cleghorn in his observations on the epidemic diseases in Minorea (1774). Hirsch states his conclusions as follows:

“Of these fifteen were confined to bodies of troops; one was in a shipyard, one in a house, and one in a prison; twelve were in a town or village (one of these, at Birmingham in 1852, being confined to children); and four were over a wider area, namely, that of 1793 on the Ligurian coast, 1847, in the Dept. du Rhône, 1858-59 in Sweden, and 1860 in the vicinity of Bartenstein. From this it follows that the pathogenesis, in the larger number of cases, is an affair of purely local influences; and the experience of several of the epidemics warrants the supposition that these influences are not infrequently of the *diætic kind*. Thus, the epidemic of 1883 in the Frankfurt garrison appears to have been set up by the use of bad pease overgrown with mold; that of 1872 among certain sections of the troops in the garrison of Wesel to the con-

tinued diet of pork and pease, the monotony of the diet having been highly objectionable to the men; again at Soest in 1874 and at Rastatt in 1878, to bad diet; among the Bavarian troops before Paris in 1871 to the monotonous diet (salt beef and mutton, with rice, but no fresh vegetables), the malady ceasing when fresh provisions arrived; among the troops in the Loureine and St. Cloud garrisons owing to the use of impure drinking water, the latter epidemic coming to a sudden end when the water was changed. In all such cases the malady appears to have been essentially of gastric origin, that is to say, associated with ordinary gastric or gastroduodenal catarrh. But for other epidemics, such as those of Bremen, Hanau, Basel, and Trebinje, noxious influences of that kind have to be excluded decidedly from the etiology. Least of all can they be alleged for those epidemics where the malady has been widely prevalent; and in cases of that kind we should probably not err if, in consideration of the circumstances amidst which the disease had arisen, we seek the cause of it in a *specific infection*."

As an instance of what he believed to be evidence of specific infection, Hirsch refers to an epidemic among the employes of a shipyard at Bremen. On account of the appearance of smallpox, vaccination of all employes was ordered. Of 1,289 vaccinated with one lymph preparation, 191 developed jaundice in the course of a few weeks, while of 587 vaccinated with other lymphs no one developed jaundice. In accordance with the belief of his time, Hirsch attributed some outbreaks to putrid effluvia from decomposing organic matter, and especially to sewer gas.

Epidemic jaundice has appeared so frequently in wars and among soldiers in garrison that it has been designated by some as camp icterus (*icterus castrensis*). Larrey met with it in Napoleon's Egyptian campaign. In 1854 there was an outbreak in a French garrison at Aniane. In 1859 it became prevalent among French troops at Civita Vecchia and a year later in a garrison of French troops at Pavia. From 1865 to 1870 there were many small epidemics in French garrisons and the disease in 1870 became highly prevalent among the Bavarian troops in the siege of Paris. In our own Civil War, epidemic jaundice is charged with being responsible for nearly 50,000 cases and quite 200 deaths. In the World War, it appeared among British, French, Italian, and German troops, though in no instance did the epidemic assume alarming proportions.

Wadsworth and colleagues report that during the summer and fall of 1921 physicians throughout the State of New York saw approximately 300 cases of epidemic jaundice, occurring in groups of from three or four to fifty or more. Attempts were made to ascertain whether or not the rats of the state were carrying *Leptospira icterohemorrhagiae*. One hundred and twenty-eight rats from various parts of the state were examined; in 22 the organism was found, and inoculated guinea pigs developed jaundice. One of the laboratory staff, while inoculating a rabbit with a virulent culture from a rat, pricked her finger with the needle of the syringe. Seven days later she developed a fever, which

continued for ten days, with a temperature fluctuating between 100° and 104° and gradually disappearing. Guinea pigs inoculated with cultures made from the blood of this patient developed jaundice.

Hiscock and Rogers report an outbreak of 69 cases at Yale University during November and December, 1921. With the exception of six cases the onsets were within a period of 15 days. The universal symptoms were weakness, loss of appetite and the characteristic jaundice. The cases were centered largely among men of rather close association. Nearly all cases reported close friends also sick. To check the significance of this, men reporting to the University Health Service for causes other than jaundice were questioned and with two exceptions they reported practically no friends sick with the disease. Some of the eating clubs had many cases quite out of proportion to the number of men served. Examination of a number of mice in the dormitories did not reveal the presence of the characteristic leptospira. As well as could be judged, this outbreak in which there was no fatal case was spread by personal contact and possibly by infection of eating utensils.

In all the records of this disease medical observers have been impressed with the fact that there are at least two forms of epidemic jaundice, one grave, the other light. This distinction is made both between epidemics and among individuals involved. In 1886 Weil described rather minutely the symptomatology and pathology of this disease in a small epidemic accompanied by great mortality, and since that time it has been the custom of many medical writers to prefix his name to the disease.

The Parasite.—It appears that the grave form of infective jaundice has long been prevalent in Japan. In 1915 Inada, Ido, Hoki, Kaneko and Ito announced the discovery of a spirochetal microorganism, which has been demonstrated to be the cause of this disease and is known as *Spirocheta icterohemorrhagiae*. These investigators think that previous workers failed to find this organism because they searched for bacteria and they expected to make their findings in the later stages of the disease, while, in truth, it has proved to be a fact that when cases come to autopsy the liver is either devoid of spirochetes or contains them in numbers so small and in forms so modified that discovery and recognition are difficult. The Japanese students searched, with negative results, the blood, urine, feces and sputum for bacteria; then they inoculated monkeys, rabbits, rats and guinea pigs with the blood of their patients. Later, they ascertained that the number of spirochetes in the blood is so small as to make their detection under the microscope quite uncertain. Their inoculation experiments showed that guinea pigs are quite susceptible. With inoculations into these animals from 17 patients, 13 positive results were obtained, the animals showing conjunctival con-

gestion, jaundice, hemorrhage, and albuminuria. It was found that the blood taken from patients on the fourth or fifth day of illness invariably gave positive results while that taken later was uncertain. In no instance did blood taken from the patient after the twelfth day of illness induce the disease in animals. The disease appears in animals within from six to thirteen days after inoculation, usually on the seventh or eighth day. Inoculation succeeds by intraperitoneal, subcutaneous, or oral injection of 2 c.c. of the blood or of an emulsion of the liver. The former is the more certain. Animals succumb to intraperitoneal inoculation within from five to eight days and to percutaneous inoculation or after administration by the alimentary canal in from nine to ten days. The typical pathologic changes in guinea pigs consist of marked general jaundice, hemorrhages into various parts of the body and parenchymatous changes in the organs. Usually the sites of hemorrhage are in the lungs, intestinal walls, retroperitoneal tissues, and the adipose deposits in the inguinal region. The liver shows cloudy swelling of the parenchyma, which is more or less colored by the altered pigment. The kidney shows an acute parenchymatous nephritis and the spleen is more or less congested and hemorrhagic. In the blood, the spirochetes are not found in the cellular elements, but in the tissues they are found in the epithelial cells. Those organs that show the most marked pathologic changes contain the largest number of the spirochetes. Comparing the changes found in the guinea pig with those seen in man, it may be said that the hemorrhage in the lungs of the guinea pig is more severe and more widespread than in man; that spirochetes can always be found in the guinea pig, which is not the case in man; and, in the liver in man the spirochetes are found in the cells, while in the guinea pig they lie between the tissue cells.

The spirochete is an irregular, wavy figure, the accurate measurements of which are not easily made. There are short forms with lengths varying from six to nine microns, intermediate forms from twelve to fifteen microns, and occasionally long individuals measuring from 20 to 25 microns. Specimens of liver or blood are fixed with absolute alcohol, methyl alcohol or osmic acid, and then subjected for two hours to a stain consisting of three drops of Giemsa solution diluted with 2 c.c. of water. Under this treatment the spirochetes become red or purplish. For vital staining, fifty per cent borax methylene-blue is recommended. In unstained specimens, the spirochetes are not visible except under dark-field illumination, when they plainly appear, showing portions which unevenly refract the light. The refractive granules vary in number from 25 to 40, according to the length of the spirochete. The organism as a whole, shows fore-and-aft, as well as lateral, movements. This organism has also a twisted motion along its long axis. When

cultures are passed through Berkefeld No. 5 filters the filtrate still carries the infection; in other words, the spirochete, during at least some part of its existence, is filtrable. The Japanese students found in their earlier work at least that the cultures of this organism grow best at between 22° and 25°, but later researches have shown that on some media they grow quite satisfactorily at 37° C.

It is quite evident from experimental work that the spirochete may enter the body through the skin or through the alimentary canal. It has been found that this organism will penetrate the unbroken skin of experimental animals. When the abdomen of a guinea pig is shaved with care that the epithelium is in no way injured and a piece of infected liver or a bit of a culture is smeared on the denuded part, the animal becomes infected. Quite naturally, infection through the skin is more certain and more rapid when there are breaks in the continuity of the tissue. So far as is known, no biting insect is engaged in the transmission of this organism. The spirochete is eliminated from the infected individual through the kidneys, from the bowels and, in some instances at least, in the sputum. The extracorporeal life of the spirochete needs further investigation. As we have said, the rat constitutes the animal reservoir.

Noguchi has shown that the spirochetes discovered by Japanese investigators are identical morphologically and serologically with the microorganisms which cause grave epidemic jaundice in Europe and America and which are found in all countries more or less widely distributed in rats. Japanese workers have prepared a serum by immunizing goats and they have employed it in the treatment of the disease. From 1 to 2 c.c. of the serum of a convalescent patient injected into an inoculated guinea pig before the appearance of jaundice prevents the development of symptoms and apparently destroys the spirochetes in the body. If immune serum is injected into inoculated guinea pigs when the spirochetes are present in the blood these organisms disappear from the blood in half an hour. It must be admitted, however, that the success which has attended the serum treatment of this disease in man still leaves much to be desired. Inada and his colleagues state that the mortality among their patients admitted before the seventh day was in those who received no serum, 57.1 per cent; in those treated subcutaneously with serum, 40 per cent; in those treated intravenously with serum, 38.5 per cent. They say that serum treatment, even when it does not lead to recovery, modifies and mitigates certain symptoms, such as frequency and severity of subcutaneous hemorrhages.

Prophylaxis.—Epidemic jaundice has frequently been confounded with yellow fever and within recent years certain very competent investigators have held that the former, like the latter, is distributed by

the bite of a mosquito; but, if there be truth in this, it is wholly lacking in demonstration. In parts of Japan where epidemic jaundice is most prevalent, competent Japanese physicians, like Inada, think that infection occurs through the alimentary canal, but admit there is weighty argument for the claim that the virus enters through the skin. This is indicated by local swellings and by enlargement of lymphatic glands. Oguro, who has practiced in an endemic area, states that he has never observed any circumstance which suggests the cutaneous mode of infection, and in his opinion the virus finds its way into the body in all cases through the alimentary canal. The class of people most frequently manifesting this disease in Japan are those who work in coal mines. Of the employes in this industry, the clerks and officials who live on the surface do not contract the disease. It has long been observed that the disease is more common in wet than in dry mines; consequently, an attempt has been made in Japan to keep the mines dry. It is also known that those who suffer from abrasions on the skin are more frequently infected than those who have no break in the continuity of tissue. So far as we know, pumping out wet mines, cautioning miners against the neglect of abrasions on the skin and against drinking water in the mines are the only prophylactic measures which have been adopted in Japan. It goes without saying that all the excretions of those sick with this disease should be thoroughly disinfected; also that we have in this disease another charge of murder against the rat. This animal thrives, fattens, and multiplies on the food it steals from man, and, in addition to being a thief, it brings into our midst surreptitiously such diseases as the plague and epidemic jaundice, not to say anything of rat-bite fever. Noguchi has prepared a vaccine, the value of which has been demonstrated successfully on guinea pigs, but it is not likely that this preparation will become largely effective in the prevention of the disease.

Mild Epidemic Jaundice.—There is no reason for assuming that all epidemics of jaundice are of the grave sort which we have just described. In assemblies, especially those of young adults, whether in civil or military life, among college students, in lumber camps, in mines, in garrisons, mild epidemic jaundice occasionally occurs. It is first seen in the eyes and gradually it tints every part of the body. The victim feels languid, tired, loses his appetite and itches (though not in all cases). The temperature may be normal, subnormal, or slightly above normal. This condition may last from a few days to as many weeks. Mild epidemic jaundice is in and of itself never fatal. It is possible that while in this state susceptibility to infection may be increased. As to the cause of this mild form of the disease, we are no fur-

ther advanced than was Hirsch who, in 1886, attributed it to dietetic disturbances.

Bibliography

- CASTELLANI, A., AND CHALMERS, A. J.: Manual of Tropical Medicine, 1919.
HIRSCH, A.: Handbook of Geographical and Historical Pathology, 1886, iii, 415.
INADA, R., IDO, U., HOKI, R., KANEKO, R., AND ITO, H.: Jour. Exper. Med., 1916, xxiii, 377; *ibid*, 1918, xxvii, 283.
MANSON-BAHR, P.: Manson's Tropical Diseases, 1921.
WADSWORTH, A., LANGWORTHY, H. V., STEWART, F. C., MOORE, A. C., AND COLEMAN, M. B.: Jour. Am. Med. Assn., 1922, lxxviii, 112.

CHAPTER XXXVII

PHLEBOTOMUS FEVER

Papataci Fever; Sandfly Fever; Three Days Fever

Description.—This is a specific fever, due to an unknown filtrable virus with which man is inoculated by the bite of a sandfly, *Phlebotomus papatasi*. The incubation period varies from three to seven days, during which there are no marked prodromal symptoms, although there may be a general weariness, accompanied by indefinite pains. The onset of this disease is sudden and is accompanied by chilly sensations, intense pain in the head, back, and frequently in the joints and bones. The face is usually flushed and the conjunctiva markedly congested. After the chill, the temperature rapidly rises, and while usually reaching a maximum of 102° , this may be extended to 105° . The pulse is only moderately accelerated and is usually proportional to the temperature, slow. The patient becomes irritable, intolerant of noise, drowsy but unable to sleep, while the sense of taste is lost and vomiting rarely occurs. There is generally a dry cough, with difficulty in bringing up a tenacious sputum. There is a well-marked leucopenia, accompanied by a marked decrease in the percentage of polymorphonuclears. There is no characteristic rash, although there may be a marbled appearance of the skin with erythematous measles-like spots. After about 48 hours the temperature begins to fall, although there may be a later slight and temporary rise. The return of the temperature to normal is often accompanied by sweating, sometimes by nose bleed and vomiting. In some instances the patient continues for a week or more debilitated in body and depressed in mind. Complications are rare, and there is no mortality.

In 1804 a three days fever prevalent in the Mediterranean region was described by Pym, and from that time on numerous English medical officers stationed in this region have written concerning the same disease. With undulant fever, it was especially prevalent in Malta during the Crimean War, at which time this Island was used as a depot and general hospital for troops both going to, and returning from, the Crimea. In the seventies of the last century it attracted the attention of Italian physicians, who made worthy contributions concerning its local existence and prevalence. About the same time it was observed among Austrian soldiers stationed on the Adriatic coast, and it was studied in a highly satisfactory manner later by Taussig. In 1906 McCarrison, writing concern-

ing a disease which he had seen in Chitral in India two years earlier, said:

“With regard to suctorial insects, sandflies are those most likely to be implicated. Their appearance corresponds in a striking way with the appearance of the disease, and the fact that they are not found where the disease does not prevail may be more than a coincidence. Experiments in my hands have, however, failed to throw any light on this point. The very great difficulties in working with sandflies may be responsible for this lack of results. * * * The use of sandfly and mosquito-proof curtains is also essential, as much for the sake of comfort as for the possible protection which may be afforded against the disease.”

In 1905 Taussig concluded from his epidemiologic studies among Austrian soldiers that the sandfly is the agent in the transmission of this disease, and in 1908 Doerr demonstrated the infectivity of the blood in this disease. In 1910 Kilroy, on the Island of Suda, exposed himself for five consecutive nights to the bites of sandflies, these insects being particularly abundant there and then. He promptly developed the fever and on the day of the chill injected some of his blood into a fellow, thereby transmitting the disease.

Geographical Distribution.—The phlebotomus is indigenous in all tropical lands, with a few possible and unexplainable exceptions, as, for instance, Bermuda. On this Island the phlebotomus is not found and there has never been known a case of the disease. The distribution of this insect over Asia extends from the Indian Ocean to the northern part of China, reaching Peking and Tientsin. In Europe it extends from the Mediterranean to middle France, embracing all the Mediterranean countries and including Switzerland, the Balkans, Greece and southern Russia. The fly is at home in apparently every part of Africa, and is especially abundant along the Nile in Egypt, in the Sudan, and in Uganda. This is true of its distribution throughout Central and South America. In the United States the phlebotomus has been found as far north as Maryland and southern Ohio. Visitors to tropical countries are likely to be infected at any season of the year, while in more temperate climates this disease and its carrier are in evidence only during the summer.

The Phlebotomus.—This is a small fly, not more than 3 mm. in length, with a body covered with long yellow hairs. The female only draws blood and, as is true in the mosquito, this seems to be a condition favorable, if not essential, to the reproduction of her kind. After being fertilized by the male, she draws the blood and retires into some damp, dark place, as a cave, cracks in stones, in walls, etc., and deposits from 30 to 80 eggs, which vary in length from 0.15 to 0.5 mm. The female deposits these eggs, which are oval and have longitudinal dark marks, singly, and from four to sixteen days, depending upon temperature,

are required for hatching. The larvae are from 2 to 5 mm. in length, are without eyes, but with a well-developed mouth. The larval stage continues, again depending upon air and temperature, from two days to two weeks. The pupal stage continues from one to four weeks, depending upon weather. The adult flies are nocturnal and are attracted by light. During the daytime they hide in cool, damp, shady places—a favorite resort is found in bathrooms and in latrines. Their size enables them to pass through the usual mosquito netting, and, in fact, to protect oneself from these pests by this device is quite impossible, because the mesh must be so fine that it is difficult to breathe through it. The sandfly feeds not only upon man, but upon most domestic animals, and it does not disdain frogs and snakes when its appetite is sufficiently urgent. Further discussion of the phlebotomus will be found in the chapter on *verruca peruviana*.

The Virus.—As we have said, the virus remains unidentified. It passes through a Berkefeld filter, and in this respect resembles the viruses of yellow fever and dengue. It is present in the blood of infected men only during the first 24 hours of illness. Apparently, the virus may be transmitted by feeding upon infected phlebotomi.

Prophylaxis.—As we have already stated, it is quite impossible for one to sleep under netting, the mesh of which is sufficiently small to keep out this insect. It is, therefore, necessary to resort to other measures. Anointing the body with repellent ointments has been recognized and a formula for such an ointment has been recommended, independently, by Balfour and Crawford. The formula for this is given in the chapter on *verruca peruviana*. Newstead recommends that breeding-places be sprayed with one per cent solution of formalin, and suggests that dark, damp places in the house might be treated in this way. He also recommends an electric fan and a modified biscuit-box trap, lined with dark cloth and placed in a dark corner in the sleeping room. Bahr says that the phlebotomus does not fly more than ten feet above the ground, and for this reason sleeping in the second story is preferable.

Bibliography

BIRT, C.: Jour. Roy. Army Med. Corps, 1913, xxi, 389. (This article contains complete reference to literature up to 1913.)

CHAPTER XXXVIII

ANTHRAX

Malignant Pustule; Wool Sorters' Disease; Splenic Fever

Definition.—Anthrax is an acute, infectious, highly fatal disease, widely prevalent among the lower animals; more rarely, and as a rule, less seriously prevalent among men.

History.—In both sacred and profane history there are many references which are supposed to relate to this disease. In the Book of Exodus (9:10), we read the following: “And it became a boil breaking forth with blains upon man and upon beast.”

Some are inclined to believe that Homer was acquainted with the disease and that it inspired the following lines (*Iliad*, B. I.):

“And first the beasts assailed he, the mule and ranging hound,
But soon at man his firebolt shot, smiting to the ground.”

Some commentators believe that the dramatic description in the *Œdipus* of Seneca refers to anthrax. The first victims are the domestic animals, afflicted one after another, until men and all beasts are being hopelessly devoured by the insatiable anger of the gods:

The sluggish ewes first felt the blight,
For the woolly flock the rich grass cropped
To its own doom. At the victim's neck
The priest stood still, in act to strike;
But while his hand still poised the blow,
Behold the bull with gilded horns,
Fell heavily; whereat his neck,
Beneath the shock of his huge weight,
Was broken and asunder yawned.
No blood the sacred weapon stained,
But from the wound dark gore oozed forth.
The steed a certain languor feels,
And stumbles in his circling course,
While from his downward sinking side
His rider falls. * * *
The abandoned flocks lie in the fields;
The bull amid his dying herd
Is pining; and the shepherd fails
His scanty flock, for he himself
Mid his wasting kine is perishing.
The stag no more fears the ravenous wolf;
No longer the lion's roar is heard;

The shaggy bear has lost her rage,
And the lurking serpent his deadly sting;
For parched and dying now he lies
With venom dried.

Another classical description is that given by Ovid (*Metam.* vii). Pliny (*Hist. Nat. Lib.* xxvi) says:

“We find it stated in the annals, that it was in the censorship of L. Paulus and Q. Marcius (164 A. D.) that carbuncle was first introduced into Italy, a malady which till then had confined itself to the province of Gallia Narbonensis (now Provence). In the year in which I am now writing these lines two persons of consular rank have died of this disease; Julius Rufus and Q. Lecanius Bassus; the former in consequence of an incision unskillfully made by his medical attendant, the latter through a wound upon the thumb of the left hand by pricking a carbuncle with a needle, a wound so small originally as to be hardly perceptible.”

Under the name of Persian fever ancient Arabian physicians described anthrax. In the ninth and tenth centuries the disease appears to have been widely disseminated over Europe. In the years 1375-1376 it is said that even wild animals died of this disease. According to Kircher, in 1617 thousands of domestic animals and 60,000 people died of the disease in central Europe. It continued to be widely prevalent in that part of the world down to the time of scientific medicine and isolated epidemics have occurred in recent years. In the sixties of the last century an outbreak in Russia was investigated by a German Commission and reported as anthrax. From 1864 to 1870 in the province of Novgorod more than 65,000 domestic animals (horses, cattle, and sheep) and 528 persons succumbed to this infection. During the latter part of the nineteenth century it became widely disseminated in South America, especially in Brazil, where it is known as “*garotilha*.” About the same time it became well established in Australia, where for some years it interfered greatly with sheep raising. It has found its way into most parts of Asia and Africa. In our own country it has appeared only as local epidemics among cattle and as isolated cases among men, known as wool sorters' disease and malignant pustule. Sobernheim gives the total number of deaths from this disease among cattle, horses, sheep, and goats in Germany in the decade from 1900 to 1909 as 55,410.

Inasmuch as anthrax is the most typically infectious of all diseases and since so many theories have been evolved concerning it, we may be pardoned for briefly reviewing the literature. As early as 1805 Kausch wrote a monograph on this disease, in which he held that it is due to paralysis of the nerves of respiration; but he offered no explanation of the paralysis. Delafond taught that anthrax has its origin in the influence of the chemical composition of the soil on the food, thus inducing pathogenic changes from malnutrition. The contagious nature of the disease seems to have

been fairly well established by Gerlach in 1845. This work was confirmed by the studies of Heuzinger and received the endorsement of Virchow in 1855, since which time it has never been questioned. However, as early as 1849 the bacillus of this disease had been seen by Pollender. This pioneer investigator did not publish his observations until 1855, but he states that they were made in the fall of 1849. First, he examined the blood of five cows dead from anthrax, and compared these specimens with material taken from the spleen of a healthy animal. The examinations were not made until 18 to 24 hours after death and Pollender states that the blood was stinking, thus indicating, as we now know, that it had become contaminated with putrefactive organisms; but the description which he gave shows that he actually saw anthrax bacilli. Pollender used a crude compound microscope made by Plossl, giving special attention to studies of the blood corpuscles, chyle globules, and the bacilli. His description of the microorganisms as he observed them may be condensed as follows: The third and most interesting microscopic bodies seen in anthrax blood are innumerable masses of rod-like, solid, opaque bodies, the length of which varies from $\frac{1}{400}$ to $\frac{1}{200}$ of a line and the breadth averages $\frac{1}{3,000}$ of a line. They resemble the "vibrio bacillus" or "vibrio ambiguus." They are nonmotile and neither water nor dilute acids, nor strong alkalies have any effect on them. For this reason Pollender concluded that they must be regarded as vegetable organisms. He was undecided whether they existed in the blood of the living animal or resulted from putrefaction, but was inclined to the former belief and thought that they might represent the infecting organism or be the bearer of the infection. It will be evident from what has been said that Pollender presented no positive proof that these rod-like bodies had any causal relation to the disease. In 1856 Brauel inoculated sheep, horses, and dogs with blood taken from animals sick with anthrax, and in this way demonstrated that the disease could be transmitted to sheep and horses, but he failed to induce it in dogs. He found sheep highly susceptible, horses less so, and dogs quite immune. He also demonstrated the presence of the bacilli in the blood of sick animals before death. It is interesting to note that he fell into error concerning the motility of the bacilli. He states that when seen in fresh blood they are nonmotile but later they become highly motile. This, as we now know, was due to contamination. It should be noted that Brauel also made examination of the blood of various domestic animals suffering from other diseases and demonstrated the absence of this bacillus in these.

In 1863 Davaine published three remarkable papers on anthrax. In the first he states that in 1850 Rayer inoculated sheep with the blood of others dead from anthrax and in this way transmitted the disease. It appears that Rayer published a short note of this work in the *Bulletin de la*

Société de Biologie in 1850, but we have not had access to this publication. Davaine's own work was of the greatest value and shows remarkable skill in technic for that time. Probably the most important experiments that he made were those in which he demonstrated that the blood of an animal sick with anthrax is not capable of transmitting the disease to others unless it contains the bacillus. It may be of sufficient interest to describe briefly the experiments which led to the demonstration of this fact. Rabbit A was inoculated with anthrax blood. Forty-six hours later, examination showed no bacilli in the blood of Rabbit A. At that time 12 or 15 drops of blood were taken from the ear of this animal and injected into Rabbit B. Nine hours later the blood of Rabbit A was reexamined and found to contain a large number of bacilli. This blood was injected subcutaneously into Rabbit C. One hour later Rabbit A died and 24 hours later Rabbit C died, while Rabbit B remained free from infection. Pasteur, De Barry, Koch, and others studied the morphology, life-history, and cultural characteristics of this bacillus, and in doing so founded the science of bacteriology.

Bacillus.—This is a long (4-10 microns), slender (1-1.3 microns) rod presenting generally square cut ends. A drop of blood from the spleen of an animal dead from this disease discloses, even without stain, great numbers of these bacteria. They are nonmotile and take the basic anilin dyes easily. Often many bacilli are attached end to end, forming what are known as bamboo rods. They are quite characteristic but do not appear in all preparations. Some bacilli show capsules which are less deeply stained and the contrast is quite striking. It is supposed that this capsule protects the bacillus against destructive action of the secretions of the body cells. At least, bacilli taken from infected animals generally show the capsules, while subcultures seldom do. It has been found that cultures grown in fluid blood serum do show the capsule. These facts indicate that the capsule results from some reaction between the organism and the blood. This bacillus will continue to live but will not multiply in the absence of air; consequently, it must be classed as an aerobe. It grows under a wide range of temperature (15° to 43° C.), but its optimum growth is at or near the temperature of the animal body (37° to 38° C.).

It grows readily on all the ordinary culture media. In undisturbed bouillon it does not produce a uniform cloudiness but appears in floccules. On gelatin plates after from two to three days at from 18° to 20° C. it develops characteristic colonies. Under a low power these are seen to be not compact, as is the case with most bacterial colonies, but loosely aggregated. The edges are not smooth and sharply defined but are more or less fringed. These are known as medusa forms and the fringe is due, as is shown under a high power, to the growth of the rods from the central mass into the surrounding medium. The bacillus produces a proteolytic

ferment, which gradually digests and liquefies the gelatin and the colonies subside into the craters thus formed. In stick gelatin cultures the bacillus grows along the line and branches off on the sides, forming a picture which has been variously designated as a brush or as an inverted pine tree; very slowly liquefaction proceeds from the surface downward. On agar plates the colonies are much like those on gelatin, with the exception that on the former spore formation may be observed. Stick cultures on agar are much like those on gelatin, with no liquefaction and a spreading of the growth over the surface of the medium. It coagulates milk and then digests the coagulum. With an abundant supply of oxygen digestion may proceed so rapidly that coagula are not seen.

The anthrax bacillus multiplies by transverse fission, but when it finds conditions of life unfavorable it does not have to strive against untoward circumstances; it simply develops seeds or spores and passes into a resting stage. In this state it does not need air or food. It is inactive and is only potentially alive. When conditions become favorable spores develop into the vegetative form. The capability of passing from one form to another is a great factor in protecting the bacillus against destructive agencies. Each bacillus produces only one spore. There is, therefore, no multiplication in the exercise of this function. The purpose seems to be solely to protect the life of the individual. When times are good, with plenty of air and an abundance of suitable food, life seems to proceed merrily and the organism multiplies abundantly. When times are hard, with inadequate food, the bacillus drops into the resting stage, in which it has no needs and awaits a change for the better. When anthrax spores are brought under favorable conditions each spore develops into a rod, which for a while carries on one end the waste remnant of the spore. Vegetative life with multiplication by fission begins anew.

There are some strains of the bacillus which apparently are not able to pass into the resting stage under any conditions. These are known as asporogenous strains. According to Eisenberg, anthrax bacilli are of two varieties or races, of different "biologic dignity;" one sporogenous and the other asporogenous, and each breeds true through all generations. However, this view is not held by all bacteriologists, and Roux gives the following method for converting the sporogenous into the asporogenous variety: Bacilli grow with a formation of spores in bouillon to which from two to six parts per 10,000 of phenol have been added. When the phenol has been increased to 20 parts per 10,000 there is no growth. Between these limits the bacilli grow without spore formation. Bacilli kept in these intermediate solutions for from eight to ten days permanently lose, even in following generations, the ability to produce spores.

The resistance of the anthrax bacillus to heat and other adverse conditions depends upon the presence or absence of spores. Anthrax spores are

among the most stable and resistant forms of pathogenic bacteria. They are more easily killed than the spores of certain nonpathogenic organisms, such as the potato bacillus. Anthrax spores on silk threads supply standards for testing the relative efficiency of disinfectants. Spores in cultures 18 years old have been found not only viable, but capable of developing into virulent, vegetative organisms. Bouillon cultures of the vegetative forms are sterilized by heat at 80° C. for one minute, while boiling for at least three minutes is necessary to insure the destruction of the spores. Dry heat at 100° C. must be continued for two hours in order to destroy the vegetative form while three hours at 140° C. are necessary to kill the spores. The effect of direct sunlight on the two forms has been studied with varying, and even contradictory, results. This is easily understood when we think of the many variable factors, such as thickness of layer, intensity of light and temperature, entering into such experiments and influencing the findings. According to Momont, drops of dried bouillon cultures, with the air temperature at from 25° to 35° C. are destroyed when exposed to direct sunlight within from six to fifteen hours in the vegetative form and after 100 hours when spores are present. The ordinary disinfectants, as generally used, destroy the vegetative forms, but are not certain in their action on spores. Geppert found that after from two to three hours in corrosive sublimate (1:1,000) all spores are not killed.

We may be thankful that this bacillus, armed as it is with so many advantages, and possessed of weapons effective against so many species of animals, has some powerful antagonists. Were this not true the world might have been depopulated by the unopposed activity of this microscopic organism. As it is, it is possible that the extinction of certain species of animals may have resulted from this infection. Many of the bacteria are markedly antagonistic and destructive to the anthrax bacillus. Chief among those in which this function has been observed and studied is the *Bacillus pyocyaneus*. In mixed cultures of these organisms the *pyocyaneus* only survives. It not only survives, but it seems to feed on the anthrax bacillus. If across a gelatin plate parallel lines be drawn alternately with needles moist with cultures of the two bacilli, *pyocyaneus* only will develop. If crosses be made with the needles the *pyocyaneus* only will develop at the cross. The *pyocyaneus* develops a bacteriolytic body known as pyocyanase, which readily digests and destroys the anthrax bacillus. This seems to be a proteolytic ferment, but unlike similar bodies it is not destroyed by prolonged boiling. This observation has led to the suggestion that it destroys the anthrax bacillus by osmotic changes. A few drops of the solution of pyocyanase added to a bouillon culture of anthrax leads to the speedy dissolution of the bacilli. Moreover, laboratory animals—sheep, rabbits, and guinea pigs, infected with

anthrax, have been cured by injections of pyocyanase. Among other less thoroughly studied antagonistic bacteria are the staphylococcus, the streptococcus, and the pneumonia bacillus.

Certain fluids of the animal body have a destructive action on the anthrax bacillus. Strange to say, this does not seem to have any marked effect on the susceptibility of the animal to this infection. The blood serum of the rabbit *in vitro* is markedly bactericidal. According to Pane, 1 c.c. of such serum will destroy 8,000 anthrax bacilli, and still the rabbit is easily susceptible to inoculation with this bacillus. The destructive agent in rabbit serum seems to be a ferment, inasmuch as it is destroyed by a temperature of 56° C. The blood of the rat, an animal which has some marked resistance to anthrax inoculation, is highly bactericidal to this organism. This is believed to be due to the relatively high alkalinity of the rat's blood. Many years ago Fodor showed that arterial blood is destructive to the anthrax bacillus.

While all mammals are susceptible to anthrax, they differ in this particular widely in degree. Epidemics are most common in cattle and sheep and the latter are easily inoculable with pure cultures, while the former are unexpectedly more resistant and require larger doses. In natural infection in both cattle and sheep, the avenue is chiefly through the intestinal tract. Algerian sheep are much more resistant than European breeds. Hogs are less susceptible than cattle and sheep, and here again there is marked variation in varieties, American and English breeds being more susceptible than those of Hungary. Among our more valuable domestic animals horses are somewhat more resistant than cattle and sheep, but in some epidemics they die in large numbers. Dogs are least susceptible but succumb to intravenous injections. Goats resemble sheep in susceptibility. Of the smaller laboratory animals, the rat is the least susceptible, while rabbits, guinea pigs, and mice succumb to every form of inoculation. It is said that a single bacillus will kill a guinea pig. All menagerie animals are susceptible. Birds are highly resistant and epidemics among warm-blooded animals are not known, but all may be infected artificially. Frogs are highly refractory but the disease may be induced in them. Snails are said to be wholly refractory. Turtles and fish are susceptible to artificial inoculation; the former readily so.

Avenues of Infection.—The virus of this disease may find admission to the animal body subcutaneously, intravenously, by feeding or by inhalation. A break in the continuity of the skin or mucous membrane may afford a port of entry. Even in feeding, the point of entry may be in the mouth, pharynx, or esophagus, caused by a slight wound. Especially is this true in animals in which superficial injuries may be caused by hard bits of food, dust, or other accidental constituents. The dried spores may infect through any of these avenues quite as effectively as the vegetative

forms. The spores are especially suitable for infection by inhalation. Moreover, in feeding, the spores are more resistant than the vegetative forms to the acid of the gastric juice. While the blood may be free from bacilli in the first stage of the disease and while in rare nonfatal cases the infection may remain localized, in most instances the blood becomes a vehicle for the transport of the bacillus and it reaches every part of the body. The organisms are eliminated from infected animals with the urine and feces. They have been found in milk drawn from sick cows a short time before death. The fetus in utero may become infected. This has been observed in both lower animals and in man. In epidemics, fields, barnyards and stalls become infected and the most common port of entry is the mouth. The feces and urine of infected animals pollute all about them and the virus is easily and quickly transferred to the well. Naturally, anthrax develops, in epidemics, among men who are brought into close contact with sick animals. In Russia from 1904 to 1909 the average annual deaths from anthrax among men numbered 16,000; in Italy from 1890 to 1900, about 2,100. In 1910 the number of persons infected with anthrax in Germany is given as 287, with 40 deaths. Certain occupations, such as butchers, tanners, sheep shearers, furriers, glove makers, shoemakers, saddlers, harness makers, dealers in hay and grain, and wool sorters, are especially exposed to this infection. The primary infection in man is most frequently through slight wounds on the skin, where malignant pustules form. The lungs may be infected through inhalation. Intestinal infection in man, though infrequent, has been reported. Fruit and vegetables may be polluted by the urine or feces of animals and may carry the virus into the alimentary canal.

Deaths from anthrax are noted each year in the U. S. Registration Area. The numbers are as follows:

1911	14	1916	28
1912	18	1917	62
1913	25	1918	43
1914	19	1919	45
1915	35	1920	39

These deaths are spread over many states. New York, by reason of its large population, usually is credited with more than any other state. There were 11 deaths in New York in 1919. Deaths in cities are frequently associated with the tanning and fur industry.

Vaccination.—In his many and varied experiments with the anthrax bacillus, Pasteur found that chickens under ordinary conditions are not susceptible to inoculation. This observation led him to suspect that the immunity of birds to this disease is due to the high temperature of their blood. By immersing chickens in cold water and maintaining them at a low temperature he demonstrated that they become susceptible. Encouraged

by this finding, he grew anthrax bacilli at high temperature for periods of several weeks, and thus prepared a modified organism which could be used as a vaccine. Generally two vaccines are prepared. The first is obtained by growing anthrax bacilli at 42.5° C. for six weeks. At this temperature the bacilli grow abundantly but never produce spores. They are not virulent for rabbits and guinea pigs but do kill mice. The second vaccine is obtained by growing bacilli at 42.5° C. for two weeks. The organism thus grown kills mice and guinea pigs but does not kill rabbits. In the immunization of cattle the first vaccine is injected subcutaneously and two weeks later the second vaccine is administered in the same way. Animals thus vaccinated are immune two weeks after the second vaccine has been administered. Immunity lasts for about a year, and in countries where this disease prevails vaccination is repeated annually.

The demonstration of the protection afforded sheep by anthrax vaccine is one of the most brilliant episodes in preventive medicine. Pasteur was being guided by his laboratory researches and by his reasoning on their significance. He was surrounded on all sides by scoffers and skeptics. The *Veterinary Press* in 1881 contained the following, "Will you have some microbe? There is some everywhere. Microbiolatriy is the fashion, it reigns undisputed; it is a doctrine which must not even be discussed, especially when its Pontiff, the learned M. Pasteur, has pronounced the sacramental words, 'I have spoken.'"

Imagine the tension of the atmosphere when Pasteur announced that he would prove his case by inoculating fifty sheep with virulent anthrax virus. Half of the sheep would be previously protected by anthrax vaccine. The other half would receive no vaccine. "The twenty-five unvaccinated sheep will all perish," wrote Pasteur, "the twenty-five vaccinated ones will survive." The plan was carried out before crowds of people comprising farmers, physicians, veterinarians, apothecaries, journalists, scientists and others. The protected sheep were vaccinated on May 5 with an attenuated virus. On May 17 a second inoculation was made with a vaccine less attenuated. On May 31 the virulent anthrax virus was given to both groups of sheep. It was the afternoon of June 2, only two days later, when the throngs again gathered to learn whether Pasteur was a dreamer or a prophet. The triumph was complete. The carcasses of twenty-two unvaccinated sheep lay on the ground, two others were breathing their last. The third died that night.

The vaccinated sheep were on their feet and in perfect health.

This demonstration created tremendous excitement throughout France. It marked a victory of far-reaching influence in the conflict which man has been waging against the adverse factors in his environment.

Horses have been immunized to anthrax bacilli and the serum of these animals used in the prevention of the disease in cattle. The antianthrax

serum is used simultaneously with or preceding the first vaccine. According to Chamberland, in 1894, 1,988,677 animals were vaccinated in France against anthrax and the loss from this disease was thereby diminished from ten per cent in sheep and five per cent in cattle to less than one per cent. Local epidemics in the United States have been stamped out in a similar manner. Neal and Chester vaccinated 331 cows in Delaware. Two of these died, giving a death rate of less than one per cent, and this occurred in a territory so saturated with the infection that it was practically impossible to keep cattle at all before the use of the vaccine. Dalrymple has been equally successful with the use of vaccine in the lower Mississippi Valley. Since the vaccine consists of living bacilli, there is always the possibility that these may become virulent and spread the disease; therefore, other precautions should be taken. When anthrax appears in a herd the temperature of every animal should be taken and those that show no fever should be removed from the barnyards and pasture-lands previously occupied by the herd. Animals dead from this disease should be burned if possible. If this is not feasible the bodies should be deeply buried and covered with quicklime. In addition and as a further precaution, the place where the animals are buried should be fenced in so as to prevent other animals feeding over it.

Anthrax from Shaving Brushes.—Soon after the war began cases of anthrax among soldiers and civilians appeared in England. From June, 1915, to October, 1916, there were 19 cases observed among civilians in England and 14 of these traced to infected shaving brushes. Up to February, 1917, 28 cases appeared among English troops in France and in 23 of these the location of the initial lesion was within the shaving area. In 1917 some 15 or 20 cases of anthrax appeared among American soldiers in this country. Six manufacturers of shaving brushes were implicated. It was found that about seventy-five per cent of a shipment of 43,200 brushes from Japan was infected. These were traced so far as possible and were destroyed. The horse hair from China and Siberia was largely infected, especially the gray and yellowish hair. Black or thoroughly dyed hair seems to have been disinfected satisfactorily. The thorough and repeated washing in hot, soapy water finally sterilizes the brush, or at least the distal ends of the hairs. In some cases infection with the anthrax bacillus induced meningitis, which, of course, always proved fatal.

The Surgeon General of the Army in his report for 1919 says that anthrax was not observed among army animals in the United States. In the American Expeditionary Force an outbreak occurred in the Third Army Remount Depot at Wengerohr, Germany. Clinical diagnosis was confirmed by laboratory findings. The disease was an acute type and caused death in seven animals. As soon as the laboratory report was

received all the animals, 10,000 in number, were treated with the Pasteur vaccine and no further losses occurred.

England has prohibited the importation of shaving brushes from Japan and other oriental countries. In addition, the Minister of Health has called attention to the desirability, and even the necessity, of sterilizing all hair employed in the manufacture of brushes in England. After the hair has been made into a brush it is difficult to sterilize it without destroying the brush. The Minister of Health in England recommends as the most trustworthy method of disinfecting hair, treatment by steam under pressure at 230° F. for at least 30 minutes. A higher temperature may seriously damage horse hair. In the United States the importation of cheap brushes from the Orient continues up to the present time (1922) and, according to Symmers and Cady, in the six years between October, 1915, and November, 1921, 36 cases of anthrax were admitted to Bellevue Hospital, ten of these undoubtedly being due to shaving brushes. These investigators purchased shaving brushes in the open market in the City of New York and found that 7.3 per cent of the brushes carried anthrax. The U. S. Public Health Service recommends that new brushes should be soaked for four hours in a 10 per cent dilution of liquor formaldehydi. During this time the temperature should be kept at 110° F. and the brush so agitated as to bring the solution into contact with all hair or bristles. It seems to us that the U. S. Government should, for the time being at least, prohibit the importation of hair, either manufactured into brushes or in the raw state, from the Orient unless all such articles be subjected to a disinfecting process known to be adequate. Smyth, after an extensive series of experiments on the disinfection of horse hair infested with anthrax, says that this can be done satisfactorily by (a) steam under pressure of 15 pounds for 30 minutes; (b) dry heat 200° F. for 24 hours; (c) formaldehyd as used in England.

Bibliography

- AMATO, A.: Sperimentale, Florence, 1921, lxxv, 327.
 BESREDKA, A.: Ann. de l'Inst. Pasteur, 1921, xxxv, 421.
 DAVAINÉ, L.: Compt. rendu, 1863, lvii.
 FRANCIS, F. D.: Mil. Surgeon, 1921, xlix, 306.
 HISS, P. H., AND ZINSSER, H.: A Textbook of Bacteriology, 1910, D. Appleton & Co.
 KOLLE, W., AND WASSERMANN, A.: Handbuch d. path. Mikroorganismen, 1912.
 MARSHALL, C. E.: Microbiology, third ed., 1921, P. Blakiston's Son & Co.
 MCFARLAND, J.: A Textbook upon the Pathogenic Bacteria and Protozoa, seventh ed., 1912, W. B. Saunders Co.
 POLLENDER, R.: Vierteljahrsehr. für ger. Med., 1855, viii.
 SYMMERS, D., AND CADY, D. W.: Jour. Am. Med. Assn., 1921, lxxvii, 2120.
 TOUSSAINT, R.: Compt. rendu, 1880, xci, 135.

CHAPTER XXXIX

RABIES

Hydrophobia; Rabies Canina; Canine Madness; Lyssa

Description.—This is a specific, infectious disease, prevalent among wolves and dogs, but transmissible to all warm-blooded animals including man. The virus is contained in the saliva of the rabid animal, whatever its species, and may be transmitted when the infected saliva comes into contact with a break in the continuity of the epithelial, cutaneous or mucous structure of any part of the susceptible animal. Most frequently, the virus is transmitted from the infected to the uninfected by the bite of the former inflicted on the latter. However, a bite is not essential, nor is it necessary that the wound through which the virus enters should penetrate the deeper parts of the cutaneous tissue. A rabid dog may infect another animal, or it may infect man by licking the hand or other part of the body where there has been only a slight epithelial abrasion. It is believed, although not demonstrated with entire satisfaction, that the so-called Negri bodies found in the brain of infected animals constitute the living virus of this disease.

In any discussion of the epidemiology of rabies it is necessary that we should know the essential symptoms of this disease as they manifest themselves in the lower animals and in man. It is needful that we give special attention to the symptoms as seen in the dog, since this animal is especially susceptible to the disease and is most active in imparting it to man and other animals.

It is a mistake to suppose that the earliest symptoms of this disease in dogs indicate a furious, raging disposition, with a tendency to attack and bite other animals or man. The development of these symptoms is gradual and the infected animal passes through a stage which might be described as one of unrest and solicitude. Usually, in the first stage the animal seeks to hide itself. It makes many vain endeavors to rest, crawling under the furniture or into out of the way corners, and places itself in one of the many attitudes of rest usually manifested by this animal; but it has no sooner placed itself in such an attitude than it seems dissatisfied with its position, shows marked inquietude, and tries to find a better resting place. During this stage the infected animal may show unusual familiarity. There is no tendency to bite, but it likes to caress other animals, and to bestow especial attention upon its master and others of the household. The agitation

and restlessness become more marked, it scatters and pulls about with its jaws and paws the material of which its bed is made or scratches and snuffles in the corners, at the doors, and against the wall. The excitement becomes more marked still, there are evident illusions and hallucinations, the dog snaps at imaginary objects in the air, advances and barks as though apprehensive of some antagonist. In this stage the voice of its master is usually sufficient to bring the animal back apparently, but temporarily, to a normal condition. In the most affectionate manner it licks the hand held out to it, but it should be remembered that even at this time the saliva contains the virus and the affectionate kisses may, if they rest upon or involve abraded patches of the skin, transmit the virus. Fleming says in regard to this stage:

“It cannot be too much or too strongly insisted upon, that, at the initial period of the disease, the dog is not really furious and mad; but is, on the contrary, as apparently harmless as usual; and that the onset of rabies is nearly always manifested by extremely benignant appearances. Not only is the animal not vicious, especially at the beginning of the malady, to those persons to whom it is attached; but, as already noticed, it would seem as if it became more than usually affectionate, and that this affection increased with the disease. Its instinct impels it, at times, to draw near to its master, as if to ask for relief from its sufferings; and, if permitted, it willingly tenders its recognition of the care bestowed on it by licking the hands or face. But these are perfidious caresses, against which every one should be warned; for, as certain as if by a bite, they may implant the virus if the animal's tongue, moist with the virulent saliva, chances to touch parts where the skin is very thin, excoriated or wounded. The smallest abrasion may be, as Bouley impressively asserts, a door opened to death; and what a death! The instances in which hydrophobia has been due to this kind of inoculation are very numerous; as people who have not been warned do not recognize the disease in the dog at this stage, and receive its Judas' kiss without suspecting the harm it may cause.”

The infected animal manifests a degree of apprehension which seems to indicate that it is thoroughly conscious of its abnormal condition and of the fact that it is likely, as its abnormality develops, to do injury to its best friends. It is apparently with the consciousness of this condition and with a fearful apprehension of what it may do, that the dog is likely, as the disease progresses in its brain, to leave its home and wander far abroad. If free, it often travels many miles, exhibiting as it goes the symptoms which are becoming more and more grave. It runs at an uncertain, but a rapid, rate, and is likely to snap at and bite any and every animal whose path it crosses. It becomes more and more vicious and flies savagely not only at other dogs, other animals and man, but attacks sticks, stones, and other inanimate objects. During such a journey the insane animal may wound, and in doing so inoculate with its virus, a great number of animals. Finally, after having traveled possibly many miles, it returns to its home, with its coat bedraggled and fouled and greatly emaciated in flesh. One who welcomes the returned

pet is likely to become infected from either a bite or a caress. Sooner or later the animal passes into the paralytic stage. Its lower jaw droops, the saliva accumulates in the mouth, and the animal attempts to remove it with its paws. The paralysis, beginning usually in the posterior extremities, gradually involves all the muscles of the body and the animal dies from asphyxiation. During the paralytic stage, on account of the fact that the animal cannot close its mouth, it does not bite, but its saliva contains the virus in large amount. Its efforts to pull the thick mucus from its throat may lead a witness to believe that the animal has a bone in its throat and to attempt to assist in its removal. Such a procedure is accompanied by great danger. The disease in dogs is invariably fatal.

The term "hydrophobia" means fear of water and is wholly inappropriate for this disease in dogs. There is at no stage of the disease in this animal a fear of water. In the first stage, and even in the second, the animal laps water with great relish and even with avidity. In its journeys it does not hesitate to wade and even to swim streams that lie in its course. Quite naturally, in the paralytic stage it cannot swallow. The unfortunate term "hydrophobia," as applied to this disease in dogs, has in many instances led to fatal infection in man. It is still a popular idea that if a suspected dog shows no terror or aversion at the sight of water it cannot be mad.

There is in some animals infected with this virus, no evidence of the first and second stages, as mentioned above. The animal is not at any time furious. It does not travel, but apparently passes into the paralytic stage from the beginning. This is what is known as "dumb rabies." The afflicted animal crawls into some out of the way place and from the beginning is unable to stand or walk. Here it lies, with its mouth open, and it may or may not have an overabundant secretion of saliva. Man often becomes infected by handling dogs with dumb rabies. The old adage, "Let sleeping dogs lie," probably comes from this.

The rabid dog has a peculiar bark, which it is difficult to describe but when well known is quite characteristic. It is neither a normal bark nor a growl, but rather a moan. The dog sits or stands with its nozzle elevated, apparently looking into space, and emits this peculiar and characteristic sound. Bouley, chief at one time of the Alfort School for Veterinary Medicine, states that two of his students while walking through the village about nine o'clock one evening heard the howl of a rabid dog proceeding from a household nearby. The howl was so characteristic that the young men were led to arouse the master of the house and inform him that his dog was rabid, which proved to be true upon an examination at the school the next morning. The old

idea that a dog baying at the moon portends some misfortune probably had its origin in this way.

It is generally believed that a foamy and abundant saliva in all cases flows constantly from the mouth of the rabid dog. On this point Fleming makes the following statement:

“This is another serious error; for the secretion of saliva is not much increased, if at all, until the disease has reached its furious stage, and before this period a dog may be quite mad without foaming or slavering at the mouth. Youatt says there is at first an increased secretion of saliva, but it soon lessens in quantity, becomes thicker, viscid, adhesive, and glutinous; and it adheres to the corners of the mouth, fauces, and teeth. It is at this period that the thirst is so ardent, owing to the inflammation or congestion at the back part of the throat. The dog sometimes furiously attempts to detach the saliva with its paws; and if, after a while, it loses its balance in these attempts and tumbles over, there can no longer be any mistake as to the nature of the malady.”

It is quite natural to suppose that in the development of its madness a dog becomes more sensitive to pain than in the normal condition. Experiment, however, has shown that this is not true and that the rabid dog becomes highly insensible to the severest torture. Such dogs have been known to fly at and seize a red hot poker and hold it in their mouths until the tissue had been severely burned. When the straw upon which it lies is set afire a rabid dog will fly away every time, but it does not seem to feel, with normal intensity at least, any injury that it may suffer. It is a popular belief, sanctioned by some able veterinarians, that a rabid dog manifests special antipathy for all others of its species and that even though it may be perfectly calm and harmless while standing at its master's side, on the appearance of another dog it will fly into a rage and attack its fellow in the most violent manner. Stories are told by eminent veterinarians going further than this and saying that a horse, cow, sheep, or any other animal bitten by a rabid dog and while suffering from the malady will attack any dog that may come into its presence. Renault tells of a horse which had been inoculated experimentally with virus from a rabid sheep and which developed rabies from this treatment. This horse, he says, was not infuriated by the presence of dogs; indeed, a dog was thrown into its manger and no attempt was made by the horse to harm the dog, but when a sheep was placed before it the horse became terribly furious, sprang upon the inoffensive animal, seized it between its jaws, crushed it with its teeth, and shook it as a terrier shakes a rat.

Not every dog bitten by a rabid fellow develops the disease. From the best statistics which have been collected on this point, it seems that about fifty per cent of dogs thus bitten develop rabies.

Another popular error concerning rabid dogs is that animals suffering from this disease will not eat. Especially during the first stage of

the development of the disease the animal may have a voracious appetite, seize and swallow without difficulty food in large lumps. In the furious stage, it may tear the food to pieces, but swallows it apparently with relish. In this stage the animal may gnaw and tear carpets, rugs, and woodwork, and may demolish its own kennel and find escape therefrom; indeed, in some instances this tendency to tear inanimate objects, to gnaw boards, or to devour straw may appear before the animal shows any inclination to attack man.

The period of incubation in the dog is quite variable, usually running from one to four or five weeks. However, there are well authenticated cases, even those of experimental inoculation, where the period of incubation has been found to be as long as ten or even fifteen weeks. Of 68 dogs inoculated experimentally by Renault, the period of incubation did not prove to be shorter than five days or longer than 118 days. In 26 cases reported by Saint-Cyr, the shortest period was 16 days and the longest 115. According to Haubner, the average period of incubation in the dog is about three months. However, compared with other reports, this is unusually long. Quite naturally, the period of incubation will depend upon the age of the dog, the part bitten, and the amount of the virus introduced. As we have already stated, this disease in the dog invariably terminates in death and in no instance has it been known to last for more than ten days. When a dog suspected of being mad can be captured without risk of its biting some one, this should be done and the animal held in captivity until its death when examination of its brain will show conclusively whether or not it had rabies. If it must be killed in order to capture it, its head should be severed and sent to a Pasteur Institute for examination. If such a dog has bitten persons it is important to determine immediately whether or not the animal was rabid, in order that the treatment of the bitten individual may be provided in proper time.

Among our domestic animals, the cat comes next to the dog in the frequency with which it becomes rabid, and this is, of course, due to the fact that it is often bitten by the dog. The relation between the cat and man is quite different from that existing between dog and man. The cat has not the intelligent appreciation of man's kindness evinced by the dog, and this shows itself even in the rabid state. There is scarcely anything more ferocious than a rabid cat. Even when imprisoned within a cage it walks with its claws protruding, endeavoring apparently to penetrate the floor. Its back is arched, its tail whips its flanks, its mouth is open and foamy, its eyes glitter; if opportunity affords it springs with feline ferocity at the face of the person presenting himself. Inasmuch as its claws are quite constantly moistened with its

saliva, its scratch is quite as bad as its bite. Some veterinarians, however, state that dumb rabies is more frequent in cats than in dogs.

Rabies is not infrequent among wild animals and is especially known and dreaded in countries where there are wolves and foxes. A pack of rabid wolves apparently knows no fear, pursues its victims relentlessly, and tears their flesh with both teeth and claws. Bites are most frequently inflicted upon the head and face, and consequently are more likely to be fatal and need prompt and more energetic treatment. It is believed by those who live in wolf-ridden countries that the rabid of this species attack man, droves of horses, flocks of sheep, and other animals, not because they are hungry but from the vicious desire to mutilate.

The vicious horse is most prone to use his heels in attacking other animals or in protecting himself from them. The rabid horse, and this animal is frequently infected where the disease prevails among dogs, uses his teeth as well as his heels. He bites his manger and the partitions and may do so with so much strength and recklessness that his jaws are broken. During times of the prevalence of rabies in a community the disease is not infrequently transmitted from horse to man. This animal suffers gradual paralysis, beginning most generally in the posterior extremities, and dies usually by the sixth day in convulsions.

Rabid cows seldom attempt to bite, but they attack both animate and inanimate objects with their horns, often with such violence that these are broken. When they are hornless they attack with their foreheads. Paralysis terminates the life of the rabid cow within from four to seven days. The symptoms evinced by goats and sheep are very similar to those observed in cattle, though the tendency to bite is more frequent among goats than among either cows or sheep. Hogs are not so frequently bitten by rabid dogs as are horses, cattle, sheep, and goats, because hogs are generally kept in pens with at least partial protection against rabid dogs. These animals die within eight days and usually earlier. There are a few cases on record in which rabies has been inflicted upon man by the bites of barnyard fowls. As we have already stated, all warm-blooded animals are susceptible to the virus of this disease.

The term "hydrophobia" is not quite so much out of place when we study the symptoms induced in man as it is when applied to those occurring in dogs. In man, the period of incubation passes into that of the active disease, with the appearance of pain in the wound or in the limb upon which the wound was inflicted. Often this is not an acute pain, but a sensation of aching, tingling, burning, coldness or numbness. By this time, as a rule, the individual is conscious of the danger to which he is subject. Depending somewhat upon his nature, he becomes

morose, uncommunicative, and despondent, or, on the other hand, irritable, excited, and restless. He does not sleep well, bright light disturbs him, and pains dart through various sections of his anatomy. Soon he finds that he has great difficulty in swallowing any kind of fluid. This discovery makes him apprehensive, he cries for fresh air and feels that he is dying of suffocation. His sensibility is intensified, the slightest noise alarms and may terrorize him, his eyes are fixed, his features contracted, and his limbs tremble. Odors imperceptible to others may greatly disturb him. There is oversecretion of a viscid, tenacious mucus in the throat and mouth. This may sometimes be tinged with blood, the sight of which adds to the alarm and terror of the patient. As a rule, the man retains his mental function and is desirous that he should do no harm to any one or transmit the disease. There are cases reported in which man is said to behave like a rabid dog, curses, howls, strikes at persons near him, attempts to bite, and finally exhausts himself through violent physical exertion. There is in man considerable fear of water, and some pathetic pictures of this condition are to be found in literature; such, for instance as the death of Charles, Fourth Duke of Richmond, who was bitten by a rabid fox in a Canadian forest in 1819. There are cases in which the sight of water or other fluids, though they could not be swallowed, had no effect upon the equanimity of the patient. There may be convulsive spasms involving both the pharynx and larynx and rendering not only the swallowing of fluids, but the inhalation of air, difficult. There may be remissions in which even the patient becomes hopeful, but the pulse becomes feeble, the skin cools, the mind wanders, exhaustion becomes more complete, and death either supervenes quietly or terminates the scene in a violent convulsion. In man the duration of the disease averages about three days, though there are a few cases reported in which the time has been lengthened to 15 or even 20 days.

The incubation period in man is widely variable, depending upon the part of the body wounded and the amount of the virus introduced. Tardieu collected 147 cases in which the incubation period varied as follows:

1 month in	26 cases
1 to 3 months in	93 cases
3 to 6 months in	19 cases
6 to 12 months in	9 cases

In the literature, one finds incredible stories both as to the brevity and the length of the period of incubation in this disease. Troillet quotes an instance in which the characteristic symptoms appeared as early as the day following the injury, and Sauvages gives the history

of a peasant who was suffering from the most urgent symptoms of hydrophobia on the third day after he had been bitten by a mad wolf. On the other hand, Chirac describes a case which developed ten years after the bite, and Finco, of Padua, lengthens this to 14 years. There are numerous other cases in the literature in which the period of incubation has been reported to extend through even longer periods. These, however, must be regarded as beyond the range of probability.

History.—It is assumed that at some time in the early youth of the human race, long before man had learned to record his experiences, certain more intelligent members of packs of wild wolves seceded from their fellows and took upon themselves and for their posterity the task of serving man as his companion and protector. In all probability lupine madness decimated wild animals before either man or his dog appeared on the earth. Be this as it may, the earliest of human records shows that rabies existed when these were made. In the books of Susruta, the earliest Hindoo works, dating about six centuries B. C., it is written that among wolves, dogs, foxes, jackals, tigers, and bears, there is a disease characterized by foaming at the mouth, snapping at and biting other animals, including man. Furthermore, it is stated that bites inflicted by these rabid animals on man lead to convulsions and death. There is in these books a recommendation that such bites should be treated by scarification and the application of boiling fats. Certain antidotes of diverse origin and nature are suggested, but the high fatality of the disease in man is emphasized. Plutarch tells us that this disease was well known in the traditions of Greece, and that it was recognized by the Asclepiadae, those early descendants of the God of Medicine. It is stated that they made records of these on the walls and tablets of the shrine visited by those seeking aid. According to Pausanius, the myth of Actaeon, the hunter who was torn to pieces by his own dogs because he discovered Diana and her attendants at the bath, is founded upon the known existence of rabies among dogs. In the Iliad, Teucer speaks of Hector as behaving like a raging dog and Ulysses says of him:

“So with a furious Lyssa was he stung.”

There have been various interpretations of passages in Hippocrates which might apply to rabies, but there is no question about the accuracy of the statement of Aristotle, who describes the disease in dogs, and, strange to say, affirms that by the bite of the rabid dog this disease may be transmitted to all animals *except* man. Furthermore, Aristotle emphasizes the certain fatality of this disease among dogs. The Jewish Talmud is said to contain indisputable records of this disease. Among the Romans there is frequent reference to the disease among both lay and medical writings. It is mentioned by Virgil and Ovid, while Pliny

collected and recorded a few facts and many fables concerning it. Celsus uses the Greek word hydrophobia and states that it is a most wretched disease in which the sick person is tormented at the same time with thirst and fear of water and in which there is but little hope. At the time Celsus wrote, there were two families in Rome whose profession seems to have been the removal of the virus from bites by suction. These operators, it appears, took proper care that they carried at the time no wounds or scars upon their lips or in their mouths, and they were accustomed to anoint these parts with oil before applying them to the wound. Celsus calls attention to the danger in applying one's lips to such wounds and, very sensibly, recommends a cupping instrument followed by the use of the cautery. In some of his other recommendations, Celsus was not so sensible. To him is attributed the recommendation that the hydrophobic patient should be thrown into water. This was with the idea of removing the morbid fear of this fluid. A translation from Celsus reads as follows:

"The only remedy is to throw the patient unexpectedly into a pond, and if he has not a knowledge of swimming, to allow him to sink, in order that he may drink, and to raise and again depress him, so that, though unwillingly, he may be satiated with water; for thus at the same time both the thirst and the dread of water are removed. But another danger arises, lest distention of the nerves may destroy the enfeebled body, being harassed in cold water; should this happen, the patient is to be taken from the pond immediately, and put into hot oil. * * * Some, after the bite of a rabid dog, immediately send the patient into a bath, and suffer him to sweat there while the strength of the body permits. In doing this, the wound is also opened, and the poison distils all the more out of it. They afterwards follow the bath with large quantities of pure wine, which is antagonistic to all poisons; and when this has been done for three days, the man appears to be free from danger. But fear of water usually arises from that wound which has not been properly attended to."

This violent water treatment, said to have originated with Celsus, was continued from time to time and under various conditions as late as the seventeenth century, when the following account of an instance of it was written by an eminent but a credulous physician of the time, Van Helmont:

"There is a castle situated by the seaside, four leagues from Ghent, which they call Cataracta. I saw a ship passing by it, and therein an old man, naked, bound with cords, having a weight on his feet; under his armpits he was encompassed with a girdle, wherewith he was bound to the sailyard. I asked what they meant by that spectacle. One of the mariners said that the old man was a hydrophobic, or had the disease causing the fear of water, and had lately been bitten by a mad dog. I asked towards what part of the sea they wished to carry him. Did they intend his death? 'Nay, rather,' said the mariner, 'He shall presently return whole: and such is the blessing of the sea, that such a kind of madness it will presently cure.' I offered them some money to take me along with them, as a companion and witness. When we had sailed about an Italian mile, the mariners did open a hole in the bottom, whereby the whole ship was almost sunk, even to the brim: indeed, they used the

brine to recoct Spanish salt, and when as that hole was now again exactly shut, two men withdrawing the end of the sail-yard, lifted up the top thereof, and bore the old man on high; but thence they let him down headlong into the sea: and he was under the water about the space of a *miserere* (1 minute and 30 seconds), whom afterwards they twice more plunged, about the space of an *angelical salutation* (10 seconds). But they then placed him on a smooth vessel, with his back upwards, covered with a short cloak. I did think that he was dead; but the mariners derided my fear, for his bonds being loosened, he began to cast up all the brine which he had breathed in, and presently he revived. He was a cooper of Ghent, who being thenceforth freed from his madness, lived safe and sound."

Among the myths concerning hydrophobia collected by Pliny was one which taught that there is a worm under the tongue of every dog. If this worm be removed from the young dog it will never become mad; if it be removed from the dog already rabid and be eaten by one who has been bitten, the disease will not result. This story had its origin in the resemblance of the frenum of a dog's tongue to a worm or to the fancied resemblance between the two. This myth concerning the worm under the dog's tongue persisted until late in the nineteenth century, and it was quite the custom among the lordly owners of kennels in England to have their pups "wormed." Strange to say, this myth has been found to be prevalent in most remote parts of the world. It was probably widely distributed before the time of Pliny. In an Anglo-Saxon manuscript, known as the Leech-Book, of the eleventh century, the following advice is given:

"Take the worms which be under a mad hound's tongue, snip them away, lead them roundabout a fig tree, give them to him who hath been rent; he will soon be whole."

The belief in the worm under the dog's tongue has been found to be widely disseminated not only in various parts of Europe, but in Africa and South America. As late as 1813 a Russian physician, Marochetti, quite stirred the medical world by claiming that in rabies, pustules appear beneath the tongue of the infected animal or man and that speedy surgical evacuation of these is essential to the cure of the disease. Marochetti stated that a Ukraine peasant called his attention to the existence of these pustules, and for a number of years medical papers were written upon the "lysses of Marochetti."

In 1872 Fleming wrote concerning the operation on the dog's tongue, as follows:

"This removal of the worm from the dog's tongue, or 'worming' as it is popularly termed, has been practiced from the days of Pliny to our own time, and is, as might be expected, a perfectly useless, nay, injurious and painful operation. Beneath the organ, in the middle, is a somewhat loose, tendinous looking fold of membrane, which constitutes what in technical language is called the 'fraenum,' or bridle of the tongue, and is designed to assist the animal in lapping. When in its ordinary relaxed condition, this fraenum looks like a small worm, and the resemblance is perhaps even more complete when it has been torn out. Hence the name of the operation, which is a cruel

one, and gives the poor dog a very sore mouth for several days, in addition to rendering the tongue less capable of performing its important functions. The supposition that this procedure will prevent a dog from becoming spontaneously rabid, or liable to infection if bitten, is excessively absurd, as the presence of the imaginary worm has no influence whatever in the production of the malady, while its absence must be a source of inconvenience to the dog, and far more likely to induce rabies than to prevent its occurrence. The operators justly deserve the punishment which will be awarded them, should they come within the cognizance of the Royal Society for the Prevention of Cruelty to Animals. Dr. Samuel Johnson, who was never at a loss for a definition, when alluding to the opinion prevalent in his time with regard to this worm, called it 'a substance, nobody knows what, extracted nobody knows why.' "

Baron Munchausen had some rivals in those who wrote on hydrophobia in the middle ages. There are many big stories, especially about the terror into which infected individuals were thrown at the mention of water or any other drinkable fluid. Eudemus tells of one, Themison, suffering from hydrophobia, entreated those who entered his room to keep at a distance, and finally tears, flowing from his own eyes, threw him into a state of raging madness when he started up and tore his garments. Some centuries later, a doctor reported a case in which his patient, supposing himself to be quite well, went to the cellar to draw a flagon of beer. No sooner did the beer begin to flow than the man was seized with terror and ran into the open with the spigot in his hand. Soranus tells us that he saw an infant, afflicted with hydrophobia, struck with terror at the sight of its mother's breasts.

Of all the Roman writers on hydrophobia the most intelligent was Caelius Aurelianus, about whose period of life there are varying opinions, with the date running from the first to the fifth century A.D. This author devotes quite a chapter to the disease and, among other things, he discusses its antiquity and comes to the conclusion that it was old at the time he wrote. He probably was the first to clearly point out that in this disease there is no fear of water among dogs and that the fear of fluid in the case of man is due to difficulty in swallowing. He speaks of the inappropriateness of the word hydrophobia and points out that difficulty in swallowing exists in other diseases. While some of his descriptions are ludicrous, the following quotation shows his good sense:

"Let the patient's chamber be tolerably warm and light; and have the part that was bitten covered with a piece of clean warm flannel. If it be necessary to bleed him, let the blood be received in the hands of the assistant, lest the noise of its falling into the basin should affect the patient. Talk to him about washing and drinking, and if he hears this without alarm, you may then give him something to drink; if not, you may let him suck through the spout of a pot, covering his eyes or darkening the room. Let his nurses be discreet and not loquacious, and have him exercised in a stretcher or sedan chair. If he refuses to take any liquid by the mouth, give it him by enema."

During the middle ages certain shrines became famous for their success in the treatment of hydrophobia. The most notable of these seems

to have been that of St. Hubert in the Ardennes. The legend was that St. Hubert, while praying at the tomb of St. Peter in Rome, was visited by an angel who gave him a miracle-working stole and a golden key. Here is the published (1671) regulation to be followed by those who sought protection from hydrophobia at the Shrine of St. Hubert:

“The afflicted person wearing the stole in honor of St. Hubert begins by confessing and fasting for nine successive days; must sleep alone either in white sheets newly washed, or else entirely dressed; must drink alone, and not bend the head down in drinking at fountains or rivers; may drink red and white wine and claret mixed with water, or water alone; may eat white and other bread; pork of a male pig not more than a year old, capons or pullets of the same age; fish having scales, such as smoked herrings and carp, and hard boiled eggs; all of which must be eaten cold, and in no other manner. The head must not be combed for 40 days, and if the person receives a wound, or the bite of any animal drawing blood, he must practice the same abstinence for the space of three days without returning. On the tenth day he must have his bandage taken off by a priest, and cause it to be burned, and the ashes cast into the piscina. He must keep the feast of St. Hubert every year, viz., on the third day of November. He may grant reprieve to all persons bitten by any mad animal from 40 to 50 days.”

So much scandal arose from the treatment of persons supposed to have been bitten by rabid dogs at the Shrine of St. Hubert that on the tenth of June, 1671, the Catholic clergy at the Sorbonne declared the practices superstitious and the claims of cures unjustified. The clergy of St. Hubert, with the approval of the Bishop of Liège and the theological faculty of Louvain, endeavored to justify their claims and to obtain permission to continue their practices. In this they were aided and abetted by one of the most prominent physicians of the time, Van Helmont, who wrote as follows:

“Our good Catholics, despairing of relief from the faculty, repair to St. Hubert, at whose shrine, by virtue of certain ceremonies, they are cured; but it is worthy of remark, if these ceremonies are not strictly observed, the latent rabies immediately breaks out, and they become irrecoverably hydrophobic. There is a vestment of St. Hubert, which is preserved in a chest, secured by six locks, the keys of which are kept by the six different vergers. For these four score years past, they have been continually cutting off pieces from this holy vestment; nevertheless it remains to this day perfectly entire. Now it is impossible that there should be any imposture in the case; for they have never been able to discover whether this miraculous robe be of linen, woolen, or of silk; consequently it cannot be annually renewed. They cut off a piece of the robe, and incarnate a thread between the skin of the patient's forehead. Hence another miracle—for a person thus cured becomes possessed of a power to postpone the hydrophobia during 40 days, in any of his acquaintance, who, after being bitten, may not have leisure immediately to visit St. Hubert; on the condition, however, that if they exceed the 40 days ever so little, without a prorogation of the term they go mad irrecoverably.”

According to James, there were in Spain as late as the eighteenth century groups of persons calling themselves *Saludadores* who pretended to

cure certain diseases, with special emphasis on hydrophobia, *por ensalmos*, or by incantation. They claimed to carry in their throats a figure of the cross, consisting of the uvula and the palate, and in the roofs of their mouths lines representing St. Catharine's wheel. They claimed that mad dogs would flee at their approach and that a good look from one of them would kill a rabid dog. James says:

"They are all great drunkards, and pretend that wine not only enables them to blow more forcibly, but also increases the virtue of the blast."

There have been from the earliest times down to the present century various recipes for the cure of hydrophobia. Some of them have been handed down from generation to generation in certain families, and since many dogs that bite people are not rabid and furthermore, since all persons bitten by rabid dogs do not develop the disease, many of these recipes have acquired great fame. Fabulous prices have been paid for their loan, and even eminent physicians have from time to time been induced to recommend them. Mead, probably the greatest English physician immediately following Sydenham, had one of these formulae introduced into the London Pharmacopeia under the name of *pulvis antilyssis*. One of the last of these nostrums, so far as we know, to find sale in the United States was the so-called "Thompson Remedy" which, as late as 1906, was made at Hyattsville, Md. The manufacturer claimed that its chief ingredient was taken from a plant which grows in South America and British India but which had not been identified by the United States Agricultural Department.

Foot castigated Mead for endorsing the nostrum, as follows:

"Dr. Mead, well known to the medical world, has written an essay on the bite of a mad dog. He has introduced it in his usual manner, with great display of reading, and hypothetical conjecture. This, like a great many more of Dr. Mead's essays, is of no other value than to shew how well he was acquainted with the writings of the ancients. * * * He has added one more imaginary prophylactic to the former stock. This he got from a gentleman of the name of Dampier, in whose family it had been kept a secret for many years. It would have been well, if it had remained there. It was first published in the Philosophical Transactions, in the year 1670, and consists of the lichen *cinerius terrestris*, in English, the ash-colored ground liverwort, and black pepper."

Fothergill recommended that the wound inflicted by the rabid animal be enlarged, packed with gunpowder, and exploded. He thought that in this way the poison would be suddenly discharged.

Hunter (John) employed the cautery, but without saving the patient, while James, Chapman and others, insisted on free excision with the knife and Chapman called attention to the fact that if the knife were introduced into the wound it would carry the virus into the surrounding tissue during the operation. There is no evidence that any surgical procedure has ever prevented death from this disease, although cauter-

ization with fuming nitric acid is still recommended and should be employed.

From the earliest times up to and even subsequent to the discoveries of Pasteur there has been an occasional writer who has held that there is in reality no such disease as rabies and that the symptoms, and even death, are due to a diseased state of the mind. This matter was discussed by Caelius Aurelianus in classical times, and he was thoroughly convinced, as he states, that "hydrophobia is a passion of the body, not of the mind." He admitted that the mind is affected, but through the body. He went further and decided that in this disease the symptoms are due to the effect of some poison upon the central nervous system. Spontaneous madness in both man and dog was believed to be possible by some most competent men even up to the time of Pasteur's discovery. In 1872 Fleming, whose work on rabies is on the whole valuable and sound, wrote as follows:

"For many years, and even now, the spontaneous origin of rabies in the species of animals in which it is most frequently witnessed has been denied by authorities who have ranged themselves on the side of the contagionists, whose belief it is that contagious diseases are propagated and maintained solely by the transmission of a specific virus from the diseased to the healthy, and that no transmissible disease ever arises spontaneously, but that its infecting element is always in existence. * * * In certain maladies which develop a contagium capable of producing the same morbid disturbance that characterizes them when transferred to healthy animals, we are almost, if not altogether compelled by the force of reasoning and the power of indisputable facts to admit their spontaneous origin from a concurrence of circumstances—many of them perhaps obscure—whose operation we are not always able to trace, save in the effects produced in the creatures subjected to their operation."

Even today there is a widely prevalent opinion that a dog may become rabid on account of the great heat of summer, especially when the animal has not an abundant supply of water and when it wears a muzzle. We still hear echoes of the old belief that muzzling dogs causes them to go mad and that they may be driven to madness by close confinement and by improper food. It is needless to add that there is no such thing as spontaneous madness or rabies in any animal, man or beast.

There were many tests of madness, some of which had the sanction of high authorities in science. The French Academy at one time directed that a piece of boiled meat should be rubbed over the gums and teeth of an animal killed on suspicion and then offered to another. It was affirmed that if the dead dog had been rabid the living animal would flee with horror from the food offered. However, as early as the sixteenth century the best authorities recommended that the suspected animal should not be killed but should be held in safety under observation and that if it had rabies it would surely die within ten days.

The possibility of the indirect transfer of the virus from the rabid animal to man has been recognized from remote times. Caelius Aurelianus tells of a seamstress who, in mending a cloak torn by the teeth of a rabid dog, wet the seams with her tongue and laid the edges of the rent with her mouth as she sewed in order that the needle might pass with more ease and in this way acquired the disease and died from it. Hildanus reports a case in which a mad dog tore the gown of its mistress but did not wound her person. The woman in mending the garment bit off the threads and in three months died from hydrophobia. Schenckius tells of a man who kissed his mad dog which was about to be killed and afterwards perished of hydrophobia. There is at least one case in which it is claimed that a boy accidentally cut himself with a knife which had been used in killing a rabid dog and which had been subsequently kept for some time protected from the light in its scabbard. The boy is said to have died from hydrophobia. Fox hunters in England long ago learned that it is necessary to thoroughly sterilize the kennels in which rabid dogs had been kept when fresh animals are introduced, and in fact, it may be stated that in many instances sterilization of kennels as practiced at that time proved to be a failure. The rabid dog was likely to spread its virulent saliva over its collar and along its leash, as well as upon surrounding objects, and in this way the new dog was likely to acquire the disease.

It must not be supposed that no real scientific information concerning hydrophobia was obtained until the time of Pasteur. Some of those who studied the disease had practiced both keen observation and experiment. It was known that in rabies the lymphatic glands are not involved and that this is quite different from what occurs in tuberculosis and syphilis. It was, therefore, argued that the virus does not travel from the point of inoculation to the brain through the blood stream, but passes along the nerve. Research went further and demonstrated by experiment that the virus is contained not only in the saliva, but in the nerves. Rossi inoculated healthy animals with emulsions of nervous tissue taken from rabid dogs and thus induced the disease. Attempts were made to study the effects of chemicals on the virus by submitting the saliva and the nervous tissue of rabid animals to the action of supposed antidotes outside the body and then inoculating animals with the treated material.

We have given this sketchy outline of the history of hydrophobia for the purpose of showing how this disease has accumulated a great variety of superstitions mixed with small grains of fact. While in number of deaths this disease does not compare with many others, its history well illustrates how for quite 2,500 years man groped through the darkness,

when, suddenly and unexpectedly, the glare of midday broke upon his vision. It is safe to say that before the discovery of Pasteur no animal, man or beast, ever recovered from this disease. Unlike most scientific discoveries, that of Pasteur in the prevention of this disease was not foretold by previous investigations. In the history of science there have been but few such brilliant and unheralded advances.

Pasteur's Work.—In 1881 Pasteur demonstrated by inoculation of animals that the virus of the disease is contained in the central nervous tissue, brain, and cord of animals dead from this disease. In 1882 he produced the disease by intravenous inoculations and showed that both kinds of rabies, the furious and the paralytic, might follow inoculation with the same virus. In 1884 he succeeded in obtaining a potent and fixed virus. This needs some explanation. Quite naturally, it was found that the virus obtained from the central nervous system of dogs acquiring the disease in the natural way and known as "street" virus was of widely variable strength. It followed from this that before strictly scientific work could be done, a virus of definite strength should be obtained in order that uniform results could be secured. Pasteur found that by successive inoculations of rabbits through about 30 individuals he was able to obtain a poison which, quite constantly, killed the animal on the seventh or eighth day; in other words, by repeated transmissions through the rabbit the action of the virus was intensified up to a definite and fairly stationary point. This is known as the "fixed" virus. Having secured this potent or fixed virus, it was necessary to find some way of attenuating its action outside the body and under conditions which can be definitely controlled. In 1885 Pasteur discovered that the virus contained in the spinal cord of a rabbit dying from inoculation with the potent or fixed preparation could be attenuated by suspending the cord in a sterilized glass-stoppered bottle, in the bottom of which caustic soda had been placed. The alkali absorbs the moisture and by keeping these bottles at a constant temperature the drying proceeds uniformly and is accompanied by progressive and regular attenuation of the virus in the tissue. A cord which has been dried in this way was found by Pasteur to have completely lost its virulence after fourteen days. A method of immunizing either man or animals to the virus of rabies was in this way established. The virus introduced by the bite of the rabid animal travels along the cord slowly and does not induce any symptoms until it reaches and accumulates in the central nervous system. If the bitten individual be treated successively day by day with emulsions of cords of different degrees of virulence the central nervous system may be made immune before the virus introduced by the bite reaches this tissue. It is much as though a man were told on the first of January that on the first of March a fatal

dose of morphin would be administered to him. The man, with this information, could begin, when told, the daily self-administration of small but gradually increasing doses of this poison and on the first of March when the fatal dose was administered to him it would not kill him. This is a brief statement of the fundamental facts established by the work of Pasteur. In 1884 Pasteur's claims were investigated by a special commission, which inoculated subdurally 38 dogs, 19 of which had been previously subjected to the Pasteur and 19 of which had had no such treatment. All the animals which had received the treatment lived, while 13 out of the 19 unprotected died from rabies within two months. Pasteur made his first human demonstration in July, 1885. The subject was a boy nine years of age who had received 14 serious bites by a rabid animal, distributed over the hands, legs, and thighs. The boy did not develop rabies.

Since Pasteur formulated his method, proceedings in the attenuation of the virus have been variously modified, but the principles remain the same. It is hardly within the province of a work on epidemiology to go into these matters in detail.

Results of the Pasteur Treatment.—While the discovery of immunization to rabies is only one of the many brilliant achievements of Pasteur, his name has become most widely and continuously known in connection with this work, and Pasteur Institutes, one feature of which and generally the most striking, is to treat persons who have been bitten by rabid animals, have been established in every part of the civilized world. In 1886 the number of persons treated at the Mother Institution in Paris was 2,671, of which 25 died. In nearly every one of these cases death was due to delay in treatment. In 1896 the number treated had fallen to 1,308, with four fatal cases. In 1910 the number treated was 401, without a death. In 1919 the number of cases treated in this institution was 1,815, with three deaths. The increase in the number treated in 1919 was in part due to the general demoralization caused by the War and in part to the closing of some of the auxiliary institutes in France and adjacent countries.

In the laboratories of the New York City Health Department from 1906 to 1919 inclusive there were 5,134 cases treated, with a total mortality of 0.39 and a corrected mortality of 0.12 per cent. It is customary to exclude from the mortality list those who develop rabies within 15 days after the last treatment, because it is believed that in these the virus introduced with the bite has been too virulent and has progressed through the nerves too rapidly to permit the establishment of immunity in the central nervous system before the poison has already reached and damaged this tissue.

On account of an outbreak of rabies in Michigan, a Pasteur Institute for the treatment of this disease was opened at the University in May, 1903. From that time up to January, 1922, 1,621 patients received treatment in this institution. In nearly every case the fact that the dog inflicting the bite was rabid was shown by the demonstration of the Negri bodies in its brain. One of the earliest patients applying for treatment at this institution came from a sparsely settled portion of northern Minnesota. It was reported that this patient developed hydrophobia and died from its effects some months after receiving treatment, but no authentic information could be secured. During the influenza epidemic in October, 1918, a patient who had received ten injections developed influenza and as a consequence of this, treatment was discontinued. This person died five days later of pneumonia, but there was a rumor that his pneumonia was complicated with symptoms of rabies. With these possible exceptions, there have been no deaths among those treated at this institution. There have been no harmful sequelae, such as paralytic symptoms. The first 780 patients received the original Pasteur treatment, consisting in the injection of emulsions of dehydrated cords. Since that time, 841 cases have been treated according to the Cumming method. The basis for this method is the destruction of the rabie virus by either formaldehyd or by dialysis. By either procedure, rabie brain is first macerated in distilled water in the proportion of 1 gram of brain substance to 100 c.c. of water. To this brain suspension, 0.24 c.c. of formalin is added, and after three hours' exposure to the action of this disinfectant, the supernatant homogeneous suspension is transferred to collodion sacs which are suspended in running distilled water. A negative test for formaldehyd indicates the completion of dialysis. Here the process of dialysis is for the purpose of removing the formaldehyd after it has destroyed the virulence of rabie virus.

On the other hand, dialysis may be used alone for the destruction of the virus. By this procedure, the attenuation and final destruction of the virus depends upon the removal of salts. This is determined by the rapidity of dialysis or the thickness of the dialyzing membrane.

The vaccine prepared by either procedure is nonvirulent. When put to the crucial test by intracranial injection, it will not produce rabies. In this respect, it differs from the Pasteur and the Högyes methods, for by these the immunization is brought about on the one hand by the injection of emulsions of attenuated rabie cords, and on the other by high dilutions of fresh rabie brain in suspensions. Notwithstanding the total destruction of the virulence of rabie virus by the Cumming method of dialysis, the vaccine so prepared confers immunity.

By the Högyes method of treatment, there is developed in rabbits,

an immunity which protects against 1.5 m.l.d.'s of fresh rabie brain suspension injected intracranially. The Pasteur method protects against 2 m.l.d.'s, and the Cumming method against 4 m.l.d.'s.

In Michigan and adjoining states the incidence of rabies constantly declined until about a year ago, since which time it has been on the increase. The establishment of the institute and the notoriety given to it, probably had something to do with the greater precautions that were taken, but recently there is evidence that the lessons of the past are being forgotten and during the past summer and fall there has been more rabies than usual. Three individuals who reached the institution after having developed symptoms of the disease died within 36 hours. In two of these the time elapsing between the bite and the first appearance of symptoms was seven weeks; in both, the bites were on the extremities. In the three cases the time between the appearance of the first symptoms of rabies and death was less than five days.

Another modification of the Pasteur treatment is that of Harris. By this method of preparing vaccine, it was found that by using Shackell's procedure for desiccation, brain and cord may be dried *in toto* without destruction of virulence. The material to be dried is placed in a vacuum desiccating jar which contains sulphuric acid. The temperature of the jar is reduced to several degrees below 0° C., by submersion in a salt and ice mixture, and a rapid vacuum is produced by suction to less than 2 mm. of mercury. The time required for the complete extraction of water by this freezing-vacuum method, is 24 to 36 hours. Rabie brain so treated and kept in vacuum retains its virulence for several months. The dried material is like chalk and is easily pulverized. It is, however, hygroscopic and after a few hours' exposure to air, becomes leathery and rapidly loses its infectivity.

Pelser (1920) has made an interesting study of the accidents and sequelae of the Pasteur treatment. He says that paralysis has followed this treatment in 163 out of 211,774 treated persons. Of these, there have been paraplegias, with the lesions in the dorsal lumbar cord; creeping or Landry's paralysis, with meningeal symptoms; indefinite neuritic forms, occasionally with slight facial paralysis, and a few cases of progressive psychoses. Even in these sequelae, however, the tendency is to recovery. Were we inclined to do so, we might question the justification of attributing these sequelae to the Pasteur treatment and ask whether they may not be due to failure to completely neutralize the virus of rabies. At any rate, fear of one of these sequelae should not deter the physician from recommending the Pasteur treatment in all proper cases. Quite naturally, it is impossible for one to speak with scientific certainty concerning the number of lives saved by this treatment, because we know that before the time of Pasteur only a vari-

able, sometimes a small, percentage of those bitten by dogs known to be rabid, developed the disease. This, however, in no way justifies any physician who is consulted by one who has been bitten by a dog either known to be or supposed to be rabid, advising against the Pasteur treatment.

The Virus.—In 1903 Negri, of Padua, found in the large cells of the nervous system certain bodies resembling protozoa, which are easily recognized in smears and sections, and which are generally believed to be the cause of the disease. These bodies have been assiduously studied by numerous investigators, among whom we may mention Williams, of the Health Department of the City of New York, who has named them *neurorrhcytes hydrophobiae*. Williams states that these bodies are found in all parts of the infectious central nervous system; that at first they are distinguished as extremely minute forms in large nerve cells as early as the fourth day in rabbits inoculated with the “fixed” virus, and as early as the seventh day in rabbits inoculated with “street” virus, and that they may be found early enough to account for the infectivity of the tissue. These bodies contain definite, well-defined chromatin masses, usually with smaller bodies of chromatin arranged about them in the form of a ring. They have the appearance of growing, multiplying organisms, but that they are such has never been positively demonstrated. It is highly probable that the Negri bodies constitute the living virus of rabies, but it is possible that they owe their existence to the action of the rabid virus on the cells of the central nervous system; in other words, instead of being the poison and causing the disease, they may be a product of the reaction between the poison and the nerve cells. At any rate, they serve a most useful purpose. It is quite well established that these bodies appear in rabies and in neither the normal state nor any other diseased condition. They are, therefore, of diagnostic value, and this is the purpose which at present they serve. There are two methods of determining whether an animal has died from rabies or has been killed while suffering from this disease. The biologic method, the one upon which sole reliance had to be placed before the study of the Negri bodies, consists in inoculating a rabbit or other animal, generally subdurally, with an emulsion of the brain or cord of the dead animal. In this procedure it was necessary to wait for a variable period, generally running from ten days to a month, but often exceeding this time, before the inoculated animal developed symptoms or until sufficient time had elapsed to justify the assertion that the suspected animal did not have rabies. The study of the Negri bodies has enabled us to dispense with the prolonged and, after all, quite uncertain biologic test. It is now sufficient to make a microscopic examination of the central

nervous tissue of the suspected animal, and usually within a few minutes or at most after a few hours by the presence or absence of the Negri bodies, to give a definite opinion concerning the presence or absence of rabies in the suspected animal. In most Pasteur Institutes, practically we may say in all, the biologic test is not applied except when there is failure to find the Negri bodies and at the same time strong circumstantial evidence that the animal whose tissue we are examining was rabid, and this rarely occurs. The nature of the virus of this disease is not definitely known and when we speak of the virus of rabies we mean the tissue or the secretion whose virulence may be demonstrated by animal inoculation. It is customary for us to say that we immunize the man or the dog, as the case may be, to rabies. Strictly speaking, this is not proper. The Pasteur treatment secures only a tolerance for the virus of rabies and a tolerance which continues for only a short time. One who has received the Pasteur treatment is not immune after a few months to subsequent bites by rabid animals, and it not infrequently happens that an individual has at intervals of months and possibly years been compelled to undergo the Pasteur treatment. This virus is filtrable and varies markedly in its resistance to the usually employed germicidal agents. Most bacteria rapidly die when placed in strong dilutions of glycerin while the virus of rabies is not affected by this agent and indeed glycerin is used as a preservative when portions of the brain or cord of suspected animals are sent to the laboratory for examination. Cumming has shown that the rabid virus is quickly and completely destroyed by formalin and this is the best agent for disinfecting or cleansing inanimate objects which have been soiled with the saliva of dogs or other rabid animals. We have already spoken in describing the Pasteur method of the attenuating effects on the virus of drying the tissue. Harris has shown that infected material may be dried completely when kept frozen without attenuating or modifying in any way the virus.

Immediate Treatment.—When one has been bitten by an animal known or suspected to be rabid the wound or wounds should be enlarged and thoroughly cauterized with fuming nitric acid. The superiority of this over other cauterizing agents has been experimentally demonstrated on animals. The dog inflicting the bite should be held in custody and if it be rabid, definite and unequivocal symptoms will develop within a few hours, or a few days at most, and the animal will die within ten days. Then its head or parts of its spinal cord should be sent to a Pasteur Institute for examination. Demonstration of the presence of the Negri bodies will be accepted as positive proof that the animal was rabid. Under these conditions the bitten person should have the Pasteur treatment without delay. The period of incubation in man, which we have

elsewhere discussed more fully, depends upon the location, penetration, and destructive action of the bite and the amount of the poison introduced. As we have stated, the poison travels along the nerves to the brain. It is quite evident that wounds on the face and head are more likely to result fatally, even with the preventive treatment, than those located on distal parts of the body. There are wounds, we might say, with great probability of truth, that are necessarily fatal whatever is done. A bite through the tongue is quite certain to end in rabies even when the Pasteur treatment is promptly and properly administered. It cannot be denied that many of those receiving the Pasteur treatment would never develop rabies even without it, but it is far better to treat many of this class than to allow one to die from the disease.

We wish to emphasize a statement already made, that rabies is a disease of animals, and especially of those belonging to the canine and feline species. The Pasteur treatment has benefited these animals more largely than it has man. Whether a dog or other domestic animal which has been bitten by a rabid one receives the Pasteur treatment or not depends upon the value placed on its life by its owner. At any rate, we should appreciate the fact that animals, as well as man, may receive and profit by the Pasteur treatment. Besides, all the preventive measures used for the protection of man against this disease are, so far as numbers are concerned, tenfold, often a hundredfold, more protective to our domestic animals.

Transmission.—The study of epidemics of rabies is certainly helpful to us in the study of epidemiology in general. Fortunately, in this disease there are no chronic carriers. Even the bite of the dog already infected does not transmit the disease until about the time the animal begins to develop symptoms. The idea that one can acquire this disease as a result of having been bitten by a dog which subsequently became rabid, is one of the many myths which have grown up in the history of hydrophobia. The rabid dog continues infective for only a short time—a few days, after which it dies.

The prolonged period of incubation in this disease is a factor which tends to render its eradication more difficult. A rabid dog in the furious stage visits a community and bites a number of animals, then returns to its home, possibly many miles distant, and dies. Even though the condition of the dog is evident and is recognized while making its journey through the community, nothing happens for weeks and possibly for months. Dogs, horses, cows, cats, and even individuals bitten by this wandering cur, possibly go on without any disturbance in health until suddenly and unexpectedly rabies develops either in animal or man. The excitement caused by the visit of the furious animal is possibly

forgotten, and now there is fully developed another center for the dissemination of the infection. It is rather interesting how closely the epidemiology of rabies—an animal disease, corresponds to that of cerebrospinal meningitis and poliomyelitis in which human beings are the carriers. In 1909 rabies appeared in southern California and during the following two years it became quite widely prevalent in the region about Los Angeles, Pasadena, and Riverside. It took three years for this disease to reach northern California in epidemic form, but scattered cases occurred throughout central and northern California even before the epidemic in southern California had reached its peak. The topography of California, as has been shown by Sawyer, Geiger and others, has given rather unusual opportunity for the study of the spread of rabies. The disease has appeared in certain valleys to which it has remained confined for months, notwithstanding the occasional transportation of dogs by railways and along other avenues. The disease was first recognized in San Francisco in October, 1911. Notwithstanding the proximity of such cities as Oakland, Berkeley, Alameda, and their environs, rabies did not immediately spread from San Francisco to these parts, because communication is wholly by waterway, but the disease did extend most speedily from San Francisco by the only land route open to animal travel, and that is southward into the counties of San Mateo and Santa Clara. There can hardly be a doubt that every day some dogs were carried across the ferry from San Francisco to Oakland, but to the rabid dog this route was, at least partially, closed and he was compelled to take the only way open to him and, as he did so, he carried the virus southward. Sawyer says that it took a century for rabies to cross the continent to the Pacific Coast and over three years for the steady march of the epidemic from the southern to the northern end of California.

Control and Eradication.—Both for preventive measures and economic reasons the number of useless dogs should be reduced. Dr. Mohler, Chief of the Bureau of Animal Industry, informs us that from data obtained in various sections of the country, it is estimated that for every 25 persons in the United States there is one dog. This makes a dog population of 4,228,425. The annual cost cannot be less than \$10 per capita, which means that we spend something more than forty millions of dollars each year on our dogs. There are three methods of reducing the number of useless dogs. One of these is by the slaughter of the excess, but this would of necessity have to be repeated annually or at least at short intervals. The second method of reducing the number is by taxation. It has been found in all countries in which a substantial dog tax has been levied and rigidly enforced that the number of dogs has been decreased and in some countries to less than fifty per cent. A

dog tax in order to be just should be graded, with a minimum assessed to the owner of one dog, and with an increase for every additional animal kept by the family. Suppose for instance, the family is taxed \$1 a year for one dog; \$2 for the second; \$3 for the third, and so on, increasing the tax with the number of animals kept. The third method is to require that all dogs kept by a family above a certain number should be desexed. In both sexes this is a comparatively simple and, under proper precautions, painless operation.

Much sentiment and little common sense have been employed in the discussion of the muzzling of dogs. There can be no doubt that if all dogs were properly muzzled when abroad, rabies would soon be exterminated. The old theory that muzzling a dog drives it to madness has been exploded; indeed, the fact that the universal muzzling of dogs in certain localities continuously for years has led to the complete disappearance of the disease in such communities was considered years ago by most competent veterinarians as positive proof that there is no such thing as spontaneous rabies. According to Hertwig, the universal muzzling of dogs in Berlin led to the eradication of this disease in that city for eight years (1854-1863). However, in May, 1863, two rabid dogs from the rural districts found their way into Berlin and within a few weeks, notwithstanding that all dogs in the city were still wearing their muzzles, between 20 and 30 cases of rabies in human beings occurred. Muzzling is inefficient unless it is universally employed. No one ever saw a mad dog wearing a muzzle and in its presence the muzzled animal is at the mercy of its antagonist unless it can escape by flight. It goes without saying that the muzzle should not harm or even greatly annoy the animal wearing it, but it must be strong enough and so applied and so constantly worn that there is no danger of its wearer biting either man or animal. By muzzling, England was freed from rabies in 1902 and for 16 years there was not a case of this disease in man or animal in that country. After its eradication in 1902, stringent measures governing the importation of dogs into England were instituted and carried into effect. No dog could be imported into that country without undergoing, at its owner's expense, quarantine for a sufficient length of time to show that it was free from the disease. Owing, however, to the extraordinary conditions arising out of the World War, this quarantine broke down and in May, 1918, an infected dog was imported and escaped quarantine. It was three and one-half months before this was known and during the latter half of 1918, 112 cases of rabies developed in dogs. This situation, according to Stockman, might have been much more serious had it not happened that most of the cases in dogs were of the paralytic form, which greatly curtailed the wander-

ings of the infected animals and their ability to inflict wounds. Twenty-one persons were bitten by these rabid animals, but all were treated by the Pasteur method and no death occurred. This outbreak gave opportunity to study the incubation period in dogs and cattle. In five cases of the former, this was found to vary from twenty-four days to seven and one-half months, and in six cases among cows it ran from 22 to 84 days. It appears that the dog showing the unusually prolonged incubation period was kept in quarantine during all this time and there seems to be no doubt about the accuracy of the observation. Although the authorities were prompt in handling this epidemic, it is evident from the appearance of the disease in Essex in September, 1919, that all rabid animals were not destroyed.

Writing in 1918 Mohler said:

"The Islands of Australia, Tasmania, New Zealand, St. Helena and the Azores have never been infected with rabies, and the first three prevent its introduction by rigid inspection and quarantine."

It is worthy of note that some years before England imposed a quarantine on imported dogs, Bardsley proposed that all dogs in England should be quarantined for a few months in order to eradicate the disease. He wrote as follows:

"The plan is as simple as I trust it will prove efficacious. It consists merely in establishing a universal quarantine for dogs within the kingdom, and a total prohibition of the importation of these animals during the existence of such quarantine. The efficacy of this preventive scheme rests upon the validity of the following propositions: First, that the disease always originates in the canine species. Secondly, that it never arises in them spontaneously. Thirdly, that the contagion, when received by them, never remains latent more than a few months. If these propositions have been established, it clearly follows that, by destroying every dog in which the disease should break out during strict quarantine, the propagation of the malady would not only be prevented, but the absolute source of the poison entirely suppressed."

The milk of a rabid animal contains the virus and may cause the disease if injected subcutaneously or intravenously, but is harmless when taken by the mouth, provided there is no break in the mucous membrane. The flesh of a slaughtered rabid animal contains the virus, but is not infectious when taken by the mouth except under the conditions mentioned above. The meat of rabid animals is condemned as unfit for food by the inspection regulations of all countries.

Mortality from Rabies in the United States.—During the 20 years from 1900 to 1919 inclusive there have been 1197 deaths from rabies reported in the expanding registration area. The deaths and rate per million population by years are shown in Table XXXVI.

As will be noted, the rates have been somewhat stationary up to 1914, since which date they have fallen to a lower level. The addition of the

TABLE XXXVI

YEAR	DEATHS	RATE	YEAR	DEATHS	RATE
1900	33	1.1	1910	64	1.2
1901	41	1.3	1911	83	1.4
1902	45	1.4	1912	74	1.2
1903	43	1.2	1913	95	1.8
1904	38	1.1	1914	65	0.98
1905	44	1.3	1915	52	0.77
1906	85	2.0	1916	36	0.50
1907	75	1.7	1917	66	0.88
1908	82	1.8	1918	63	0.77
1909	55	1.1	1919	58	0.68

southern states to the registration area could hardly have been responsible for this decline, as might be the case with certain diseases such as scarlet fever and diphtheria, which are more prevalent in the north, for the deaths are as common in the south as elsewhere. The wider use of the Pasteur treatment is probably responsible for the decline.

Bibliography

- BABES, B.: *Traite de la rage*, Paris, 1912, J. B. Bailliere.
- BIGELOW, H. R.: *Hydrophobia*, Philadelphia, 1881, D. G. Brinton.
- CUMMING, J. G.: *Jour. Infect. Dis.*, 1914, xiv, 33.
- DOLAN, T. M.: *The Nature and Treatment of Rabies or Hydrophobia*, London, 1879, Bailliere, Tindall, and Cox.
- FIELDER, F. S.: *Jour. Am. Med. Assn.*, 1916, lxvi, 1300.
- FLEMING, G.: *Rabies and Hydrophobia: Their History, Nature, Causes, Symptoms, and Prevention*, London, 1872, Chapman and Hall.
- FOOT, J.: *An Essay on the Bite of a Mad Dog*, London, 1788, T. Becket.
- FORCHHEIMER: *Therapeusis*, New York, 1915, D. Appleton & Company.
- GEIGER, J. C.: *Jour. Am. Med. Assn.*, 1917, lxxviii, 513.
- GILMAN, J. A.: *A Dissertation on the Bite of a Rabid Animal*, London, 1812, Richard Taylor and Company.
- HAMILTON, R.: *Remarks on the Means of Obviating the Fatal Effects of the Bite of a Mad Dog, or Other Rabid Animal, etc.*, London, 1785, J. Johnson.
- HARRIS, D. L.: *Jour. Infect. Dis.*, 1912, x, 369; *Jour. Am. Med. Assn.*, 1916, lxxvii, 923.
- HARRIS, D. L., AND SHACKELL, L. F.: *Jour. Infect. Dis.*, 1911, viii, 47.
- JAMES, R.: *A Treatise on Canine Madness*, London, 1760, J. Newbery.
- LAYARD, D. P.: *An Essay on the Bite of a Mad Dog*, London, 1768, J. and F. Rivington.
- MARIE, A.: *L'étude expérimentale de la rage*, Paris, 1909, O. Doin.
- PARRY, C. H.: *Cases of Tetanus and Rabies Contagiosa, or Canine Hydrophobia*, London, 1814, Richard Crutwell.
- PELSE, W. A.: *Ztschr. f. d. ges. Neurol.*, 1920, xxii, 121.
- REID, R.: *On the Nature and Treatment of Tetanus and Hydrophobia, with Some Observations on a Natural Classification of Diseases in General*, London, 1817.
- THATCHER, J.: *Observations on Hydrophobia*, Plymouth (Mass.), 1812, Joseph Avery.
- VIALA, J.: *Ann. de l'Inst. Pasteur*, 1920, xxxiv, 412.

CHAPTER XL

RAT-BITE FEVER

Sodoku; Sokiosa (Japanese)

Description.—The saliva of many animals contains organisms which, when introduced into man's body percutaneously, may cause the development of infectious diseases. Since man is more likely to be bitten by small rodents than by most other mammals, it is not at all strange that such bites should be followed by general infection. Such diseases have most frequently resulted from the bites of rats, though there are cases which have followed wounds inflicted by the bites of squirrels, weasels and ferrets, and the bites and scratches of cats. It is not at all likely that the organism thus introduced into the body of man from all these species or even from the same species, at all times and in different countries, is the same. Rat-bite fever has apparently a widely variable period of incubation—from one to 60 days, though usually from 21 to 28 days. In some cases the wound inflicted by the bite has healed before there are any generalized symptoms. In other cases the wound remains unhealed and there may be ulceration and even gangrene. The acute symptoms are ushered in by a chill, when the temperature may run as high as 105° , while the pulse becomes feeble and rapid. At a variable time after the chill a purple erythematous eruption occurs and may spread widely over the body. The lymphatic glands, especially those in the axilla, become enlarged and painful. After the fever has continued for a variable period, usually of four or five days, the temperature becomes normal and the patient apparently recovers; but after a period, which is also variable, there is a relapse and these intervals of pyrexia and apyrexia may continue for months and possibly for years. The apyrexial intermissions may occupy only a few days or may extend through much longer periods. According to Kusunoki, there may be one or two yearly relapses extending through ten years. Hora reports a case which showed about ten relapses annually for a period of 17 years, and Kitagawa and Mukoyama saw a case in which recurrences continued for 15 years. They conclude from this that the immunity against the virus is incomplete, and they suggest that the causative agent belongs to the protozoa. In Japan the mortality from this disease is about ten per cent and death results either from exhaustion in childhood or old age, or complications in adult life. The testimony concerning the efficiency of arsphenamine and its congeners in the treatment of this disease is contradictory. This is true also con-

cerning the response to the Wassermann test. In our opinion, these facts suggest that the virus is not the same in all cases.

History.—It seems that rat-bite disease has been long recognized in Japan, but it did not receive the attention of western medical men until near the close of the last century, when attention was called to it by articles by Katsura and Miyake. In 1908, according to Hora, Japanese physicians reported 30 cases. However, more than 40 years before this time a case was reported in the United States, and in more recent years reports have come from widely separated localities on every continent.

Row says:

“That rat bite produces a disease *per se* was known to the ancients in India. Thus, in the writings of Wagabhatt, Shushrut, and a treatise called Yogaratnakarone, one finds full description of the etiology and symptomatology of this disease. For the purposes of this memoir a reference to the writings of Wagabhatt, who flourished 23 centuries ago, will be sufficient. This ancient savant, amidst a descriptive account of the symptoms of a general irregular recurrent type of fever, a well-marked asthenia and anemia, refers to the cutaneous lesions produced by rat bite—and these when translated read as follows: Burning in the patches. Nodular and urticarial eruption; petechial and even hemorrhagic patches on the body: edematous condition, discoloration and even ulceration of the nodules: lividity of the mucous membranes and hemorrhages.”

The Virus.—Ogata believes the causative agent to be a sporozoon, while Schottmüller attributes it to a streptothrix, designated as *S. muris ratti*, of which Blake subsequently obtained a pure culture and with which he was able to induce local inflammation and proliferative lesions in rats at the site of inoculation. Of two cases examined by Tileston one showed in blood smears streptothrix which could not be demonstrated in the other. Litterer has reported a case occurring in Tennessee, in which he found a streptothrix sufficiently different, in his opinion, from that described by Schottmüller to be classified as a new species. Tunnicliff calls attention to the great similarity of the streptothrix in the bronchopneumonia of white rats to that isolated in cases of rat-bite fever, and she suggests that if wild rats suffering from streptothricial bronchopneumonia should bite man the disease might be conveyed in this manner. Bahr defines rat-bite fever as follows:

“An acute febrile disease caused by a spirochete, *Leptospira morsus-muris*, inoculated into man by the bite of an infected rat, causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapses, and, in some cases a cutaneous eruption.”

This leptospira, as obtained from the infected animal, is short, measuring from two to five microns. In artificial cultures it grows much longer, reaching 20 microns. It is most easily found in blood by means of the ultramicroscope. It has also been obtained from the exudate surrounding the bite and from the fluid expressed from infected lymph glands.

Mice, white rats, and guinea pigs are highly susceptible, though animals usually survive, and the organism can be detected in the blood serum about seven days after inoculation and it persists in this fluid for months. The three common species of rat are susceptible, and this is true of the ferret and the cat. According to Bahr, three per cent or thereabouts of the house rats in Japan carry this infection. Futaki and his coworkers (1916) detected in the involved glands and in the tissue about the bite, a spirochete from nine to ten microns in length. In another case they found spirochetes measuring only from two to six microns. These findings have been confirmed, with variations in the length of the spirochetes, by several Japanese investigators, most of whom have come to the conclusion that the short and long spirochetes belong to the same species, the differences in length being in part due to age and in part to the medium in which the organism is grown. It has been shown by Ido, Ito, Wani and Ôkuda that the serum of individuals who have recovered from rat-bite disease contains a substance which, when injected into the abdomen of a guinea pig with *S. morsus-muris* dissolves or destroys this organism; in other words, it responds to the Pfeiffer test. These demonstrations render it highly probable that *S. morsus-muris* is the causative agent of at least some of the rat-bite cases occurring in Japan, but they do not prove that this organism is identical with the virus or viruses carried by other rodents and capable of being transmitted to man. Neither do they show that this organism is the specific cause of the rat-bite fevers that occur in different parts of the world.

Cases of fever following bites and scratches of cats have been reported not only in Japan, but in other parts of the world, notably in Italy. In 1914 Schottmüller described a disease in a woman who had been bitten by an African squirrel, *Taraxerus cepapi*. The same squirrel bit a man. In the woman there was a fever, accompanied by the formation of ulcers, as a result of which the sight of one eye was destroyed. In the pus taken from the man Schottmüller found a nocardia, but he was of the opinion that this organism played no part in the production of the disease.

Row gives the following description of the spirochete found by him in cases seen in Bombay:

“(1) The spirochetes derived from the human lesion are identical with those recovered from the peripheral blood of the white mouse or guinea pig infected with the human material. (2) The Bombay spirochete is smaller than even the small variety of Futaki and the small type of Kitagawa and Mukoyama and practically of uniform size. (3) The broad distinction made by Futaki in the long and short forms according to the situations the virus is derived from, (viz., long form from lymphatic nodules and short ones from peripheral blood) does not hold good in Bombay where all that are found are short and 1.5 to 2 microns in length, any slightly longer forms detected being distinctly division forms of the same. (4) These are found only in the cutaneous lesions and not in the peripheral blood of the Bombay cases. (5) No lymphadenitis

has been noticed in all the cases under observation. (6) I have not been able to satisfy myself as to the presence of terminal flagella although the ends of the Bombay spirochete are pointed. (7) The behavior of the Bombay spirochete to experimental animals is different from those of the Japanese type. In mice and guinea pigs it produces a low type of infection, the spirochete being demonstrated even six months after the infection, the animals being apparently quite well, although one guinea pig and one white rat succumbed to the infection nearly three months after the infection, and 15 days respectively. (8) With all these differences, the interest to the record here given seems to me the strong connection with and the identity of the spirochete derived from the human cutaneous lesions resulting from rat bite and the organisms recovered from animals infected with the material derived from the human lesion."

Crohn, of New York, has collected 52 cases of this disease as found in the literature, including 14 American cases. This by no means covers all the recorded cases, but it is interesting to read Crohn's summary after his rather exhaustive study. This runs as follows:

"What is the nature of the disease? Are we dealing with the results of a living parasite, transmitted from the rat to man by means of a bite, or is this a disease caused by the implantation of a peculiar and highly toxic substance.

"In the nature of its course it resembles most clearly relapsing fever, the febris recurrens of the Asiatics and Europeans. The diseases resemble each other in the intermittency of the symptoms; the incubation period in both is variable. In its favorable reaction to salvarsan the disease has a common factor with both syphilis and relapsing fever, but more particularly with the former. The finding of a spirochete as the cause of both these latter diseases suggests this as the etiological factor in this malady. In the prominence of the nervous symptoms and the post-febrile paralyses, rat-bite fever recalls relapsing fever. The one reported postmortem examination in this disease revealed a serous meningitis, with increase of cerebrospinal fluid. The irregular paraplegias and atrophies recall the tabetic lesions of lues. * * * Many of the symptoms of this malady might be the result of a powerful toxin elaborated at the site of the wound and transmitted along the regional nerve paths to the central nervous system, in a manner similar to the propagation of the toxin in tetanus. The extension of the toxin to the posterior ganglions might again recall the dysphagia symptoms analogous in rabies. In the light of a case reported by Banker, the possibility of a neurotoxin, locally created, must be considered. Banker remarks on the permanent atrophy and paralysis of the arm only, following on the bite of the hand of the same limb."

Prophylaxis.—The bites of rodents should be opened and thoroughly cauterized.

Bibliography

- BAHR, P. H.: *Manson's Tropical Diseases*, Seventh Edition, 1921, p. 217.
 BLAKE, F. G.: *Jour. Exper. Med.*, 1916, xxiii, 39.
 CROHN, B. B.: *Arch. Int. Med.*, 1915, xv, 1014.
 FUTAKI, K., TAKAKI, F., TANIGUCHI, T., AND OSUMI, S.: *Jour. Exper. Med.*, 1916, xxiii, 249.
 HORDER, T.: *Quart. Jour. Med.*, 1910, iii, 121.
 KITAGAWA, J., AND MUKOYAMA, T.: *Arch. Int. Med.*, 1917, xx, 317.
 LITTERER, A. M.: *Jour. Tennessee Med. Assn.*, 1917, x, 310.
 ROW, R.: *Bull. de la Soc. de Path. Exotique*, 1918, xi, 188.
 SCHOTTMÜLLER, H.: *Dermat. Wehnschr.*, 1914, lviii, Supplement, p. 77.
 TILESTON, W. J.: *Jour. Am. Med. Assn.*, 1916, lxvi, 995.
 TUNNICLIFF, R.: *Jour. Am. Med. Assn.*, 1916.

CHAPTER XLI

SNAKE-BITE

Ophidismus

Geographical Distribution of Poisonous Serpents.—In North America there are representatives of two families of poisonous snakes, Crotalinae and Elapinae. Of the Crotalinae, there are two groups, one with and one without, rattles. The rattlesnakes are divided into two genera, *Crotalus* and *Sistrurus*. Some of the more common species of rattlesnake will be briefly described as follows: (1) *C. adamanteus* or *C. durissus*, diamond-back rattlesnake; maximum length eight feet; head broad and distinct from neck; grayish-green with diamond markings; southeastern United States from North Carolina to Louisiana; pine forests and swamps; nocturnal; feeds upon rabbits, birds, and rats; does not seek to escape when disturbed by man. (2) *C. atrox*, western diamond rattlesnake; maximum length about seven feet; color varies in different localities through different tints of gray; Texas, New Mexico, Arizona, and southern California; most vicious. (3) *C. scutulatus*, mountain diamond rattlesnake; maximum length about three feet; Texas, Arizona, and New Mexico. (4) *C. ruber*, red diamond rattlesnake; maximum length five feet; arid regions of the southwest. (5) *C. confluentus*, prairie rattlesnake; maximum length about six feet; color some shade of green or olive; north-western part of the continent from British Columbia to Mexico, extending eastward into the Dakotas, Nebraska, Kansas, and Texas. (6) *C. horridus*; banded or timber rattlesnake; maximum length about four feet; some shade of yellow or olive; from Maine to the Rocky Mountains; quite frequent in the mountains of Pennsylvania; during the hibernating season members of this species coil together in masses, but scatter in the spring. (7) *C. oregonus*, Pacific rattlesnake; maximum length less than four feet; from British Columbia to southern California, extending eastward into Idaho, Nevada, and Utah; found up to altitudes of 12,000 feet. (8) *C. tigris*, tiger rattlesnake; maximum length less than four feet; some shade of yellow or gray; desert regions of Arizona, New Mexico, Nevada, and southern California. (9) *C. molossus*; black-tailed rattlesnake; New Mexico and Arizona. (10) *C. cerastes*, horned rattlesnake; maximum length less than three feet; brown, yellow, or pink; Utah, Arizona, Nevada, and eastern California. (11) *C. lepidus*, green rattlesnake; maximum length about two feet; along Mexican Border.

The most common of the genus *Sistrurus* are: (1) *S. catenatus*, mas-

sasauga; maximum length about five feet; some shade of brown; swampy localities throughout the northern United States and Canada; feeds upon cold-blooded animals; eats well in captivity and has been much used in the study of snake venom. (2) *S. miliarius*; pigmy rattlesnake; maximum length less than two feet; some shade of gray; along the Gulf Coast, extending northward into Arkansas and Tennessee.

Of the *Crotalinae* without rattles there are two genera, *Ancistrodon* and *Lachesis*. The most important representatives of the genus *Ancistrodon* in North America are the following: (1) *A. contortrix*, the copperhead, deaf adder, pilot snake, upland moccasin; maximum length about three feet; some shade of brown; widely distributed over the United States and Canada. (2) *A. piscivorus*, water-moccasin or cotton-mouth; maximum length five feet; some shade of brown with darker bars or markings; often found lying in bushes and on limbs above water, into which they drop when disturbed; widely distributed over the United States and Canada.

Of the *Elapinae*, there are in North America at least two species, *E. fulvius* and *E. euryxanthus*. The former is known as the harlequin snake, is beautifully colored—red, yellow and black rings, with iridescent epidermis. The colors are clear-cut and striking like those of minerals. The second species is known as the Sonora coral snake and is red with yellow-rimmed black rings. There has been much difference of opinion as to the poisonous nature of these coral snakes, but there can be no doubt that the species here referred to is highly poisonous. There are several species of nonpoisonous snakes, such as the scarlet king snake, the red king snake, the ringed king snake, and the scarlet snake, which resemble the poisonous coral snakes. *E. fulvius* is widely distributed over the United States south of the Ohio and the Missouri Rivers and over Mexico and Central America.

Most of the poisonous snakes of South America belong to the genus *Lachesis*, of which there are in that country nearly thirty known species. One of the best known and most deadly is *L. lanceolatus*, the Fer de lance of Martinique or the jararacussu of Brazil; maximum length about six feet; coloration variable; found throughout a large portion of Central and South America and in some of the West Indian Islands. In Martinique it still causes a considerable number of deaths each year.

In Europe there is only one family of poisonous snakes, and of this only one genus and five species. The best known is the common European viper, *Vipera berus*. This is a small snake, generally about two feet in length; in different localities the color varies through tints of gray, yellow, brown, and red; nocturnal in its habits and found most frequently along hedges and by piles of stone; distributed from the British Islands through middle and northern Europe to the eastern shores of Siberia; its bite is seldom fatal to adults, but occasionally so to children.

In Asia and Africa every family of poisonous serpent is known. Some of the more important are the following: (1) *Naja tripudians*, cobra di capello; formidable and dangerous and is said to cause several thousand deaths each year in India; its habitat extends from the Transcaspiian, through China, into the Philippines and Formosa, all through India, into the Malay Peninsula, and the Dutch East Indies. Among certain classes in India it is still regarded as a crime to kill a cobra when it enters a home, as it often does in searching for rats. Food is offered the unwelcome visitor and even when the people themselves are starving to death a repast for the *Naja* is always prepared and ready. (2) *N. bungarus*, king cobra or hamadryad; may reach a length of 15 feet; may attack and even pursue man. Its bite may kill an elephant within three hours. We quote from Calmette the following statements concerning the king cobra:

“Indian legends relate that Brahma, having descended on earth and fallen asleep one day at high noon, a *Naja* placed itself in front of him and, dilating its broad neck, procured for him kindly shade. In order to repay it for the service rendered, Brahma gave *Naja* the marks that it bears on its neck, intended to frighten the kites and other birds of prey, which are implacable enemies of this snake. When a native of the Malabar Coast finds a *Naja* in his dwelling, he begs it in a friendly way to depart; if the request be without avail, he offers it food in order to attract it outside; if the snake still does not move, the Hindoo goes in search of the pious servitors of one of his divinities, who, procuring an offering, address the most touching supplications to it. * * * The hamadryad is dreaded with good reason, for not only is it aggressive, and hurls itself boldly upon its adversary, but it also pursues him, a trait exhibited by no other poisonous snake. Cantor relates that in Assam an officer met with several young hamadryads which were being watched over by their mother. The latter turned toward its enemy, who took to his heels with all speed, pursued by the terrible reptile. The course taken led to a river, which the fugitive did not hesitate to swim in order to gain the opposite bank, hoping thus to make good his escape; all, however, to no purpose. The snake still pursued him, and the officer saved himself only by a stratagem. He dashed his turban on the ground; the snake threw itself upon it and savagely bit it several times, thus giving the officer time to reach a place of safety.”

N. bungarus is widely distributed throughout India, but is not so frequently seen as *N. tripudians*. The former has the reputation of eating not only small mammals, birds, and fish, but of feeding upon other snakes. It is believed by some Hindoos that the king cobra calls other snakes about it and then falls upon and devours them. We cannot believe that this is anything more than a superstition. There are several species of *Naja* in Africa. *N. haje* is the common hooded cobra of Africa known as the Aspis. It is also designated the spectacle snake on account of certain markings on the neck. Colors vary in different localities, generally running from brown to black and yellow. It is common in Egypt, in the Sudan, and in the Sahara Desert. It often reaches a length of six feet, possibly more, and is vicious.

Another hooded snake of Africa is *Scpedon hemachates* or the spitting snake. It is said by natives of Africa that this snake throws its venom into the eyes of the man who attacks it. This story has been corroborated by European travelers, but Calmette, who kept one of these animals for some time in his laboratory never observed it spitting or throwing its venom.

One of the most common and most dreaded snakes of India is *Bungarus candidus*, known to the natives as the krait. It is a small reptile, reaching at most only about three feet in length; inclined to enter porches and houses and hide itself in most unexpected places. The bite of the krait is fatal to dogs within a few hours, and it is regarded, next to the cobra, as the most dangerous snake in India.

The deaf adder, *Bitis arietans*, which is yellow or orange and with difficulty distinguished from the sands upon which it lies, is a deadly viper, whose habitat covers practically all of Africa. There are numerous species of this genus and they vary in length from five feet or more to less than one foot.

The Hydrophinae, or sea snakes, abundant in the Indian Ocean and in parts of the Pacific, are all highly poisonous. There are about 50 known species and it may be said that they are more or less abundant in all tropical seas.

In Asia and Africa there are representatives of every known species of poisonous snake, with the exception of the rattlesnake which is exclusively an American product.

Venoms.—The first to experiment with snake venoms, so far as we can ascertain, was Fontana, who, in 1767, published an elaborate book on this subject, which was subsequently translated into English. This learned priest obtained the venom by cutting off the heads of snakes, dissecting out the poisonous glands, and extracting their contents. He used more than three thousand vipers and submitted more than four thousand animals to their bites. He concluded that all warm-blooded animals are susceptible. In 1843 Bonaparte (Lucien) studied the chemistry of venoms and came to the conclusion, which has been substantiated by all subsequent research, that the poisonous principle is a protein body. In 1858 Mitchell (S. Weir) began a series of researches, which continued with more or less interruption through 30 years and a final report on which was made by Mitchell and Reichert in 1886. The findings of Mitchell and Reichert may be summarized as follows: The active principles in snake venom are in solution; the formed elements in venom, consisting of bacteria, epithelial scales, and tissue debris, are not harmful; in the dried state venoms retain their toxicity indefinitely; even absolute alcohol has no effect upon their poisonous properties; they are soluble in glycerin and may be kept in this menstruum quite indefinitely; their poisonous constituents are pro-

teins, of which there are two groups, globulins and peptons; in some venoms there are three kinds of globulins; the proportion between globulin and pepton varies in the venoms from different species; venom when introduced into living tissue induces marked necrotic changes,—in this respect there is no other poison comparable to it; it reduces the red-blood corpuscles to formless colloid matter and renders the blood incoagulable; when brought into contact with the vascular tissue of a warm-blooded animal it so alters the walls of the capillaries that the blood passes through; this phenomenon is wholly unlike that of inflammation, inasmuch as in the latter only the white-blood corpuscles pass through the capillary walls; it is due to the action of the venom on the walls of the capillaries that hemorrhages follow snake bites; some venoms cause extensive hemorrhages, while others have no such effect; the hemorrhagic action is due to the globulins; the peptons are more active in the production of edema, in the breaking down of the tissues, in the production of putrefaction and sloughing; peptons have little power to produce ecchymosis, to prevent coagulation or modify the capillary walls of the blood vessels; they have less tendency to accelerate the pulse; they tend to increase the blood pressure by irritating the capillaries, and are the principal factor in exciting the peripheries of the vagi nerves in the production of the increased respiration rate; in venom poisoning, death may occur through paralysis of the respiratory centers, paralysis of the heart, hemorrhages in the medulla, or possibly through the inability of the profoundly altered red corpuscles to perform their functions; the differences between the proportions of globulins and peptons and differences in kinds in both of these are accountable for the diverse symptomatology and pathology resulting from the bites of different kinds of snakes; there is no reason for supposing that either the globulins or peptons are identical in their chemical composition or physiologic action in venoms from different species of snakes; cobra venom does not produce the marked lesions of crotalus poisoning, because it is lacking in globulins; it is weak in the production of the local swelling and blackening of the parts, of the ecchymosis, of the altered corpuscles and of the noncoagulability of the blood; the pepton of cobra venom has a more decided power in producing convulsions than that of the rattlesnake.

Mitchell and Reichert close their report made in 1886 with the following paragraph:

“The fact that the active principles of venom are proteids, and closely related chemically to elements normally existing in the blood, renders almost hopeless the search for a chemical antidote which can prove available after the poison has reached the circulation, since it is obvious that we cannot expect to discover any substance which when placed in the blood will destroy the deadly principles of venom without inducing a similar destruction of vital components in the circulating fluid. The outlook then for an antidote for venom which may be available after the absorption of the

poison, lies clearly in the direction of a physiological antagonist, or, in other words, of a substance which will oppose the actions of venom upon the most vulnerable parts of the system. The activities of venoms are, however, manifested in such diverse ways and so profoundly and rapidly that it does not seem probable that we shall ever discover an agent which will be capable at the same time of acting efficiently in counteracting all the terrible energies of these poisons.''

While subsequent investigators have worked out numerous and valuable details concerning the chemistry and physiologic action of snake venoms, no fundamental error has been found in the work of Mitchell and Reichert. More recent students state that their globulins are albumoses, but this is due to change in nomenclature and does not modify the nature of the symptoms. In 1886 a protein substance soluble in dilute saline solutions, insoluble in concentrated saline solutions, insoluble in pure water, and nondialyzable, was called a globulin. Such is the nature of one of the poisonous proteins obtained from snake venom by Mitchell and Reichert. They called it a globulin; in 1886 they could have called it nothing else. Because it is now called an albumose does not change its chemical properties or its physiologic action. In 1886 Mitchell and Reichert reported certain substances in snake venom which are soluble in water, in dilute saline solution, and are dialyzable, as peptons. At that time they could have called them by no other name, and the fact that some one now designates them as syntonins does not alter either their chemical composition or their physiologic action. Within recent years the tendency has been to classify the poisonous constituents of snake venom by the effects upon animals rather than by chemical differences. We now speak of the neurotoxins, the hemorrhagins, the hemolysins, and the hemagglutinins of the venoms. This does not mean that we know anything more about the chemistry of the toxins of snake venoms than we knew when we employed the chemical terms; in fact, we may be justly accused of attempting to hide our ignorance of the chemistry of snake venoms by the adoption of the pathologic term. On the whole, it may be said that the neurotoxins correspond to Mitchell and Reichert's peptons, while the hemorrhagins correspond to their globulins. Cobra venom is very rich in the pepton-like proteins and the bite of this snake is followed by marked edema around the wound and without hemorrhagic infiltration; on the other hand, the venom of the rattlesnake is rich in globulin and the bite of this snake is followed by extensive hemorrhages. It is now customary to designate those snakes whose venom is rich in neurotoxins (the peptons of Mitchell and Reichert) as colubrines; while those whose venom is rich in hemorrhagins (the globulins of Mitchell and Reichert) are designated as viperines.

Natural Immunity.—It is well known that certain animals are able to

cope successfully with most venomous snakes. The mongoose stands at the head of these animals. Calmette makes the following statement:

“I first introduced a mongoose into a cage containing a *Naja bungarus* (*Ophiophagus*) of large size. The snake rose up immediately, dilated its hood, and struck savagely at the little animal, which, darting nimbly out of the way, escaped being seized, and, frightened for a moment, took refuge in a corner of the cage. Its stupor, however, was but of brief duration, for at the very moment when the hamadryad was preparing to strike at it again, the mongoose, with open mouth and snarling, sprang upon the reptile's head, bit it hard in the upper jaw and crushed its skull in a few seconds. This scene is in every respect reminiscent of the admirable description given by Rudyard Kipling in his celebrated ‘Jungle Book’ of the great war that *Rikki-tikki* (the mongoose) fought with Nag (the cobra) ‘through the bathrooms of the big bungalow in Segowlee cantonment.’”

This observation led Calmette to take blood from mongooses, mix it with the venom of the snake, and inject the mixture into rabbits. He found that the blood of the mongoose exhibited antitoxic power which, though evident, was of little intensity and insufficient in all cases as a certain preventive of death. Then it was found that a mongoose is able to stand, without apparent injury, four times the dose lethal to a rabbit. With six times this dose the mongoose was ill for two days, then recovered, but with eight times the lethal dose the mongoose succumbed in 12 hours. In view of these experiments, Calmette says:

“It must be concluded from these facts that the West Indian mongoose is but little sensitive to venom; that it is capable of withstanding, without malaise, doses which are considerable in proportion to its size, but that its immunity is far from being absolute. If it is generally the victor in its combats with poisonous snakes, the result is mainly due to the extreme agility with which it is endowed.”

In a fair fight a rat will often kill a large snake. Acton and Knowles write:

“A perfectly fresh and angry cobra, three feet six inches in length, and a big rat were placed together in a large cage where both had full liberty of movement. We expected that the cobra would bite the rat immediately. After a furious fight which lasted 15 minutes the rat, which was still untouched was allowed to escape unharmed. The cobra which was suffering from 14 wounds inflicted by the rat,—including wounds of both jaws and one eye,—died from shock. It was for this reason that in all these biting experiments both rat and cobra had to be held.”

Cushny, having obtained an extra large old white rat which he thought would be a satisfactory meal for his large massasauga, placed the rat in the cage with the snake. Both stood at attention, one at each end of the cage, for a few seconds, when the rat gave a leap, grabbed the snake through the head, and killed it instantaneously. The rat evidently received no wound, and the ability of this animal to combat the snake is due to the greater intelligence and agility of the former.

The blood of the rat contains no antitoxin to the venom of the snake and when bitten by the snake it shows no great resistance to the action of the venom.

It is well known in this country where rattlesnakes abound that hogs frequently devour them and suffer no harm. Calmette injected a dose of cobra venom sufficiently large to kill a big dog, under the skin on the back of a pig without harm. This investigator found that the blood of the pig contains no antivenin and concludes that the immunity possessed by the pig is due to the fact that its skin is lined with an enormous layer of adipose tissue which is but slightly vascular and in which absorption takes place slowly.

According to Phisalix and Bertrand, hedgehogs hunt vipers and devour them with great greediness. These observers demonstrated that the hedgehog will withstand 40 times the amount of snake venom necessary to kill a guinea pig. However, in its contest with a viper the hedgehog generally escapes being bitten, but when bitten it may succumb.

Certain birds, notably the heron, feed largely upon snakes, and it has been suggested that in snake infested districts these birds be legally protected. At present they are killed for the brilliancy of their plumage. Through all historical times in countries where poisonous snakes abound there have been people who make their living by handling these reptiles. Among the ancient Romans snake-charmers were known as *Psylli*. Clot Bey writes as follows concerning the Egyptian *Psylli*:

“The *Ophiogeni*, or snake-charmers, have been renowned from all time. Strabo speaks of them and Prosper Alpinus was a witness of the singular effects of their art. The majority of modern travelers who have visited Egypt have been equally struck with the freedom with which they handle poisonous reptiles and animals. The *Psylli* go from house to house calling forth and charming the snakes that they may happen to contain. They claim to attract them by means of a particular power. Armed with a short wand, they enter the chamber to be purged from these venomous guests, make a smacking noise with their tongue, spit upon the ground and pronounce the following incantation: ‘I adjure you, by God, if you are without or within, to appear; I adjure you, by the greatest of names; if you are obedient, appear! If you disobey, die! die!’ The snake, submissive to this command, departs forthwith, issuing from a crack in the wall or floor.”

Plutarch says that immunity to snake venom was inherited by the *Psylli* and that they exposed their children to serpents as soon as they were born in order to determine legitimacy of the child and the fidelity of the wife.

In India snake-catchers, venders, and charmers constitute a caste of Hindoos known as *Mal*. In France, especially in the mountainous regions, there are those who become quite skilled in catching and handling the small vipers, the only poisonous snakes existent in that country.

It is said that these people are careful to be bitten once a year by a young viper. There have been various explanations of the apparent exemption from the action of the venoms shown by snake-charmers and handlers. Calmette who has looked into this question rather minutely, says that the methods pursued by the snake-charmer in order to protect himself are varied. In the first place he makes himself thoroughly familiar with the habits and movements of the snake. He has learned by long experience to anticipate every movement and to avoid every threatened strike. There is no virtue in any of the preparations which he wishes to sell and to which he attributes his boasted immunity. In some instances, the poisonous fangs of the snake exhibited have been drawn. Some have a real immunity acquired by having been previously bitten repeatedly by young snakes. In some localities, undoubtedly a form of vaccination is practiced. In the valleys of the Orinoco and the Amazon and among certain tribes in central Africa a dried poisonous fang is used in this procedure; with it two or three minute incisions are made, and the slight wound is dressed with various herbs and preparations which are supposed to give immunity. A Portuguese, Pinto by name, has reported a vaccination to which he submitted, on the east coast of Africa. The natives obtain the venom of the common snake of that region, make it into a viscid paste with vegetable substances, and with this the vaccination is made.

“Two parallel incisions, five millimeters in length, are made in the skin and into these is introduced the paste containing the poison. These incisions are made on the arms, near the junction of the radius and ulna with the carpal bones, on the back of the hand, on the back, on the shoulder blades, and on the feet near the great toes. * * * After undergoing this operation my whole body was swollen up for a week, and I underwent every possible kind of suffering. I have never been bitten by any snake, and cannot vouch for the infallibility of this remedy.”

Artificial Immunity.—In 1887 Sewall reported a series of experiments which have proved to be fundamental to all the brilliant and useful discoveries in the production and use of antitoxins. This investigator, employing the venom of the massasauga (*Sistrurus catenatus*), determined the minimum fatal dose for pigeons. Then, beginning with a small fraction of this dose and gradually increasing the amount, he was able to so immunize pigeons that within a few weeks they bore without harm ten times the minimum lethal dose for the control. Sewall found that when the injections were discontinued the birds gradually lost their immunity, but six months after the last injection they still showed marked resistance. Following these investigations, Ehrlich immunized animals to the toxins of certain vegetable poisons, those of the castor and jequirity beans.

In 1893 Kaufmann immunized animals, following Sewall's method,

to the venom of the small French viper, but he did not succeed in producing a greater tolerance than three times the minimum lethal dose. About the same time, Phisalix and Bertrand, at the Paris National History Museum, and Calmette, at the Paris Pasteur Institute, began experiments which demonstrated that in inducing immunity in animals to snake venom the immunizing principle is generated in the blood of the treated animal, and with the serum of such blood, immunity could be passively transferred to other animals. Phisalix and Bertrand employed the venom of the European viper. Solutions of this were heated at 75° C. for five minutes and given as first doses. These were followed 48 hours later by a dose of the venom not heated. Calmette worked with coral cobra venom, which he diluted with a one per cent solution of hypochlorite of lime.

“By degrees the quantity of venom is increased and that of the hypochlorite progressively diminished, and the injections are repeated every three or four days, while attentively following the variations in weight of the animals. The inoculations are suspended as soon as emaciation supervenes, and resumed when the weight becomes normal again. After four injections of chlorinated venom the hypochlorite is omitted and a direct inoculation made with one-half the minimum lethal dose of pure venom; then, three or four days afterwards the injection is increased to three-fourths of the minimum lethal dose; and finally, after the lapse of another three or four days, a lethal dose is injected. * * * As a rule three months are necessary for the vaccination of a rabbit against 20 lethal doses. In six months we can succeed in making it very easily withstand 100 lethal doses.”

Calmette's work was soon confirmed by Fraser, of Edinburgh, and within a few years institutes for the preparation of antivenin were established at Lille, France, where Calmette did his work; at Karauli, India; in Philadelphia; in Sao Paulo, Brazil, and at Sydney, Australia.

Calmette was fully aware of the fact that the active principles in the venoms of different species are not identical, and consequently, an antivenin prepared with one venom would not be efficient in the treatment of bites by other snakes. In his book on the subject (1908) he wrote:

“The venom of Colubridae in general is characterized by the constant predominance of *neurotoxin*, to which it owes its extreme toxicity, which is especially intense in the case of cobra venom. It contains no, or scarcely any, *hemorrhagin*; for this reason local symptoms of poisoning by Colubrine are almost *nil*. This *neurotoxin*, as we have seen, shows itself very highly resistant to heat.

“The venom of Viperidae, on the contrary, especially that of *Lachesis*, is characterized by the almost total absence of *neurotoxin*, while its richness in *hemorrhagin* is considerable. Consequently heating for a few minutes at 75° C. renders it almost entirely negative, since *hemorrhagin* is very sensitive to heat.”

Calmette prepared polyvalent antivenins. His animals (horses) were first immunized to cobra venom in order that they might successfully

withstand the neurotoxin. Afterwards these animals were treated with viperine venom. At present it is customary to prepare specific antisera against the bites of the poisonous snakes most prevalent in the country where they are to be used. In India specific sera against the cobra and against the vipers found in that country, especially Russell's viper, are prepared. In Australia, Tidswell has prepared a specific antivenin against the bite of the *Notechis scutatus*. This antivenin has a marked protective power against the bite of this species, but is not of value in the treatment of bites inflicted by other Australian poisonous snakes, such as the deaf adder. A specific serum against the bite of the rattlesnake has been prepared by Flexner and Noguchi. It was found that this preparation neutralizes the effects of *Crotalus* venom, but has no action against other venoms. In 1904 Noguchi prepared two specific antivenins, one for *Crotalus adamanteus*, the other for *Ancistrodon piscivorus*. In Brazil specific antivenins have been prepared against the bites of the *Fer de lance* and the South American rattlesnake.

Antivenin, quite naturally, has not proved the great success that has been won by diphtheria antitoxin. In the first place, the accidents and complications which occur in immunizing horses and goats in order to obtain the antivenin are numerous. A comparatively long time is required, many animals are lost in the procedure, and there is great trouble with sloughing sores, especially when an antivenin to the bites of vipers is being prepared. In the second place, it is difficult to secure concentrated antivenins, and in the third place, if the antivenin is not used within a few minutes after the bite has been inflicted it is ineffective and, as a rule, those bitten by snakes are not at the time near sources of supply of antivenin.

Acton and Knowles have recently (1913-1916) published a most exhaustive study of snake-bite. Their conclusions may be condensed as follows. The active principle of cobra venom is a neurotoxin which is thermostabile, bearing a temperature of 100° C. for ten minutes; the chief active constituent of the venom of Russell's viper is a protein, which begins to lose its toxicity at 65° C. and has completely lost it at 85° C.; these toxic elements are not definite chemical substances, but are complex in character and are modified in their activity by heat; the venoms of snakes are modified salivary secretions and contain all gradations of proteins from albumins to peptons; viperine venoms are much richer in coagulable proteins than are colubrine venoms; the neurotoxin of cobra venom is absorbed with great rapidity, but is fixed in the nerve cells in a relatively slow process; viperine venom is, on the other hand, absorbed slowly but on entering into the circulation is rapidly

fixed to the endothelial cells of the blood vessels; with cobra venom the union of neurotoxin and brain cell is a loose one and can be dissociated; with viper venom the union with the endothelial cell is firm and cannot be dissociated; after a cobra bite some delay in the administration of the antivenin may occur and life still be saved; in the case of viper bite the administration of antivenin must follow within a few minutes in order to be of service; all antivenins are relatively weak products compared with standard diphtheritic and antitetanic sera; *in vitro* the value of standard antivenins is for cobra venom, 1 c.c. equals 1 mg., for viper venom, 1 c.c. equals 2 mg.; the relative effectiveness of methods of administration of antivenin are in the following order—subcutaneous, intraperitoneal, intravenous; the antivenin is a globulin, or behaves like a globulin, retaining its full potency up to 65° C.; the venom—antivenin complex is a precipitin reaction; the union of venom with antivenin takes place instantaneously; a constant dose of antivenin when acting *in vitro* upon increasing doses of cobra venom neutralizes more and more venom; an increasing dose of antivenin acts *in vivo* upon a constant dose of cobra venom, each extra c.c. of antivenin given neutralizes less than the c.c. before it; the law of incomplete or reversible mass action holds true for the union of venom and antivenin; the administration of a given dose of antivenin in intermittent half-hourly doses in cobra bite gives approximately as good results as does the administration of the whole dose in a single injection; in order to save life not less than 100 c.c. of a specific antivenin should be given at once intravenously; by applying well-known methods of concentrating the potency of weak antidiphtheritic sera, weak antivenins have been concentrated from seven to ten times their original potency against cobra venom; in case of bite apply a firm ligature, preferably with three-eighths inch rubber tubing; impregnate the area of the bite with a hypodermic injection of a solution of gold chlorid; inject from 100 to 200 c.c. of antivenin, preferably specific, intravenously.

Prophylaxis.—A live wideawake population would soon free any country from poisonous snakes. Even in India, Europeans and intelligent natives are seldom bitten by snakes. They do not go barefoot, but wear heavy shoes, with the legs protected by puttees. They do not sleep on the ground and their houses are not open to the ingress of serpents. When walking at night they carry lanterns, and it is worth mentioning that most of the poisonous snakes are nocturnal in their habits and a large percentage of their strikes in the daytime miss their aim, but the native Indian has his superstition about snakes and believes that some great harm will befall him if he kills them.

Bibliography

- ACTON, H. W., AND KNOWLES, R.: *Indian Jour. Med. Res.*, 1914-15, ii, 46, 91, 110; 1915-16, iii, 275.
- CALMETTE, A.: *Venoms*, London, 1908, John Bale, Sons & Danielson.
- FAYRER, J.: *The Thanatophidia of India*, London, 1872, J. & A. Churchill.
- KAUFMANN: *Les Vipères de France, Morsures, Traitements*, Paris, 1893.
- MITCHELL, S. W.: *Collective Miscellaneous Writings*, Smithsonian Publications, 1881-86.
- MITCHELL, S. W., AND REICHERT, E. T.: *Researches Upon the Venoms of Poisonous Serpents*, Smithsonian Institution, Washington, 1886.
- NOGUCHI, H.: *Snake Venoms*, Carnegie Institute, Washington, D. C., 1909.
- PHISALIX AND BERTRAND: *Compt. rend. d. l'Acad. d. Sci.*, 1894, cxviii, 285.
- SEWALL, H.: *Jour. Physiol.*, 1887, viii, 203.

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